ACC22 WRAP-UP

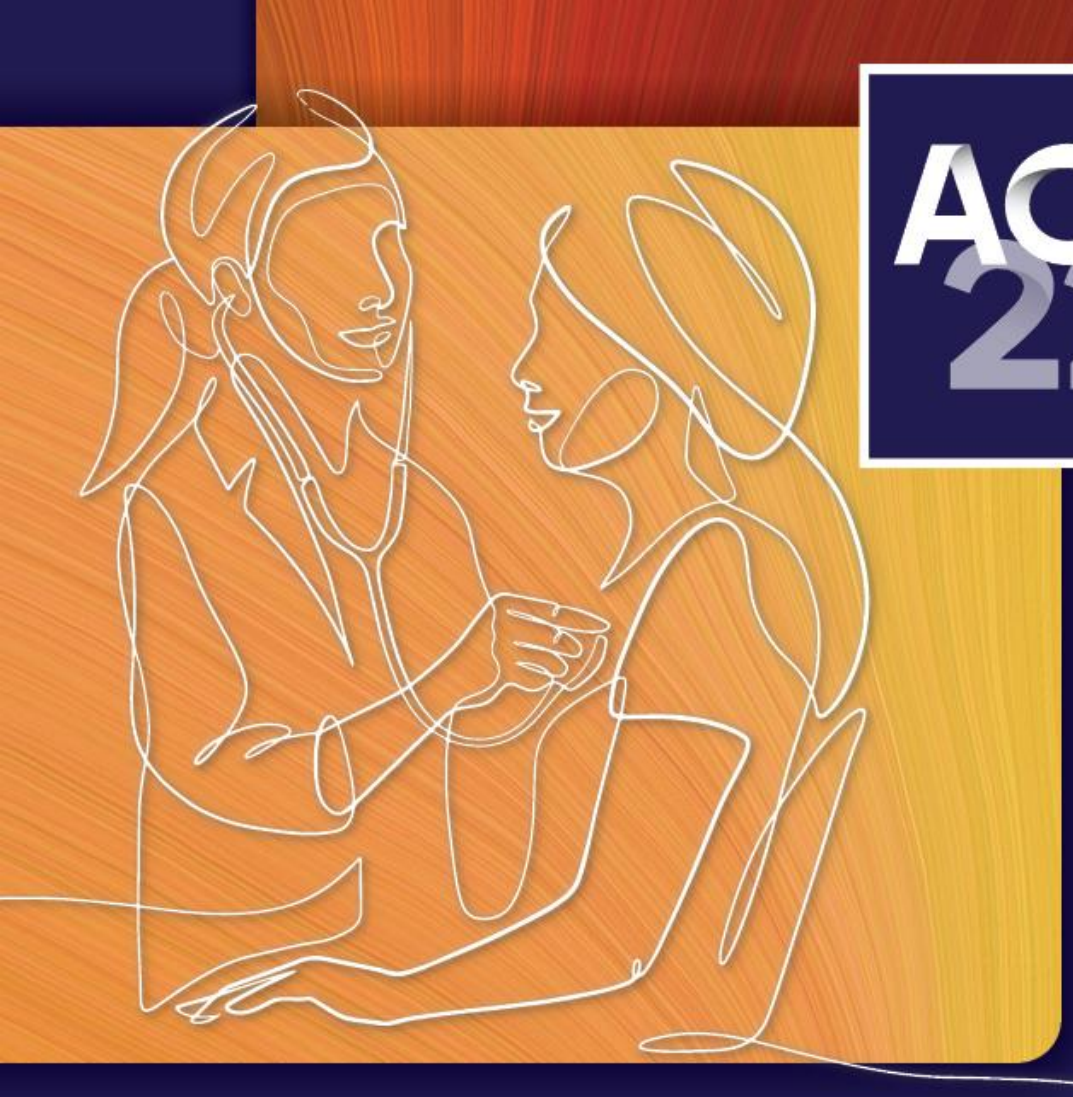
ACC 22
APRIL 2 - 4
WASHINGTON, DC

Presented by:

Madjid Chinikar, M.D

Ehsan Khalilipur, M.D

Cardio_Cast



ACC 22

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

EDIT-CMD trial

Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in Patients with Angina and Non Obstructive Coronary Arteries

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Disclosure statement of financial interest

I, Tijn Jansen, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

The EDIT-CMD trial was sponsored by research grants from Abbott

Background

- Up to 40% of patients undergoing coronary angiography for stable angina do not have obstructive coronary artery disease (ANOCA)[1]
- In 60-90% coronary vasomotor dysfunction (CVDys) is the underlying pathophysiology[2]
- CVDys consists of two major endotypes[3]
  - Coronary artery spasm
  - Coronary microvascular dysfunction (CMD)
- Both endotypes can be assessed by coronary function testing (CFT)
- ANOCA patients have a worse prognosis, and adequate therapy is paramount[4]

1 Johnston, EHJ 2011 2 Suda, JACC 2019 3 EAPCI expert consensus, EHJ 2020 4 Jespersen, EHJ 2012

Background

- Guidelines recommend the use of calcium channel blockers (CCBs) to reduce symptoms in Coronary vasomotor dysfunction[1]
- Diltiazem is one of the most frequently prescribed medications in these patients[2,3]
- However, these recommendations are based on dated, small, non-randomized trials[1]
- The effect of diltiazem has never been evaluated in ANOCA patients in a blinded placebo controlled randomized trial

1 Knuuti, EHJ 2020 2 EAPCI consensus document, EHJ 2020 3 CorMicA trial, Ford, JACC 2018

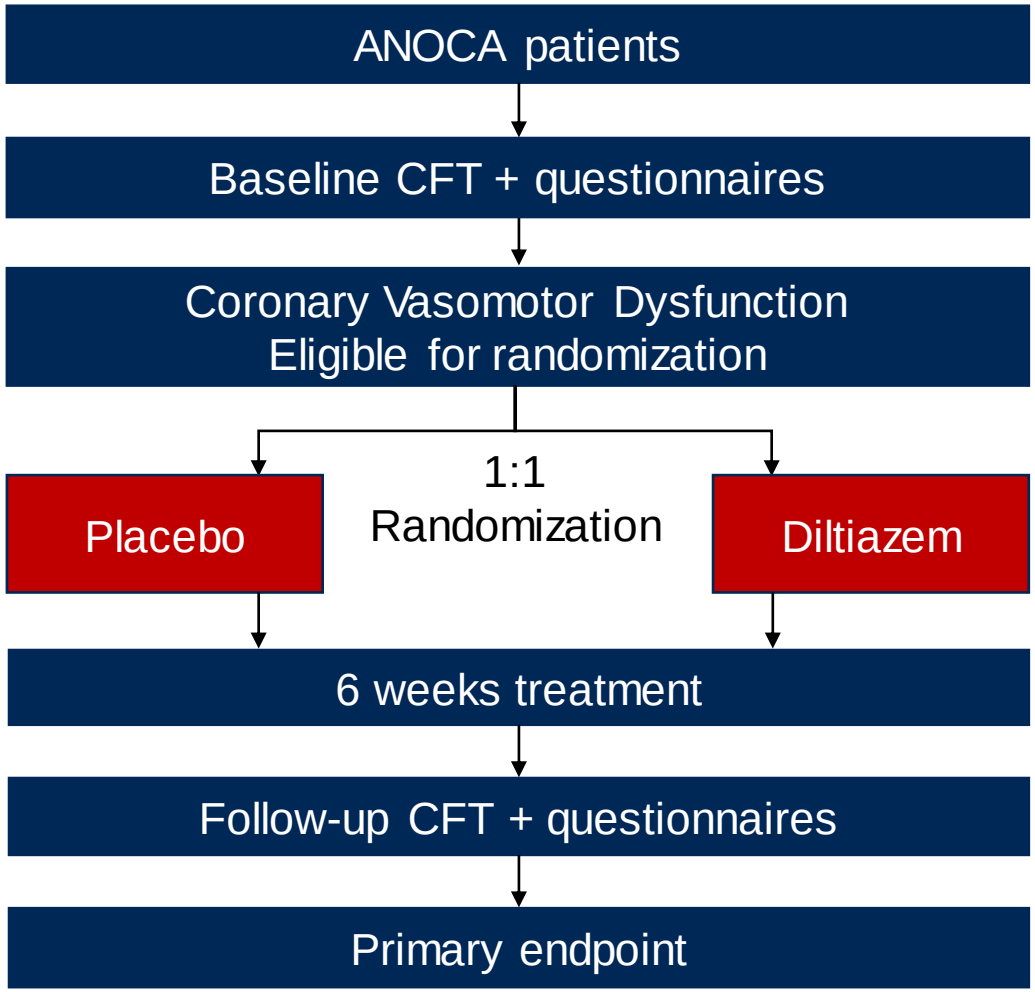
Objective

- EDIT-CMD: randomized, double blind, placebo-controlled trial

- **Primary objective:**
  - To determine treatment success of diltiazem on coronary vasomotor dysfunction as assessed by repeated coronary function testing

- **Secondary objective:**
  - To assess the effect of diltiazem on symptoms and quality of life

Trial design



Trial organization

Principle Investigators

Suzette Elias-Smale, Niels van Royen, Annemiek de Vos, Pieter Smits.

Data Safety Monitoring Board

Freek Verheugt (chair), Eric Boersma (statistician), Nico Pijls (clinical expert)

Trial statistician

Steven Teerenstra

Study coordinator

Regina Konst, Tijn Jansen

Radboudumc university medical center

MAASSTAD ZIEKENHUIS een santeon ziekenhuis

catharina een santeon ziekenhuis

Key in- and exclusion criteria

Inclusion criteria

- ✓ Age >18 years
- ✓ Chronic angina (≥ 2x/week)
- ✓ No obstructive CAD (< 5 years)
  - CAG: < 50% stenosis, or intermediate stenoses (50 - 70%) with FFR > 0.80 or iFR > 0.89
  - CCTA: finding of non-obstructive coronary arteries

Exclusion criteria

- X Use of CCB < 2 weeks
- X Contra-indication to coronary function testing:
  - Contraindication for adenosine, acetylcholine
  - Ongoing dipyridamole treatment.
- X Contra-indication for treatment with CCB
- X Other cause of angina deemed highly likely by the treating physician.
- X LVEF< 50%; PCI < 3 months; history of CABG; Surgically uncorrected significant congenital or valvular heart disease, cardiomyopathy or myocarditis; eGFR < 30; significant hepatic impairment; Pregnancy; life expectancy < 1 year.
- X Symptomatic hypotension or systolic BP < 100 mmHg at screening visit on 2 consecutive measurements.

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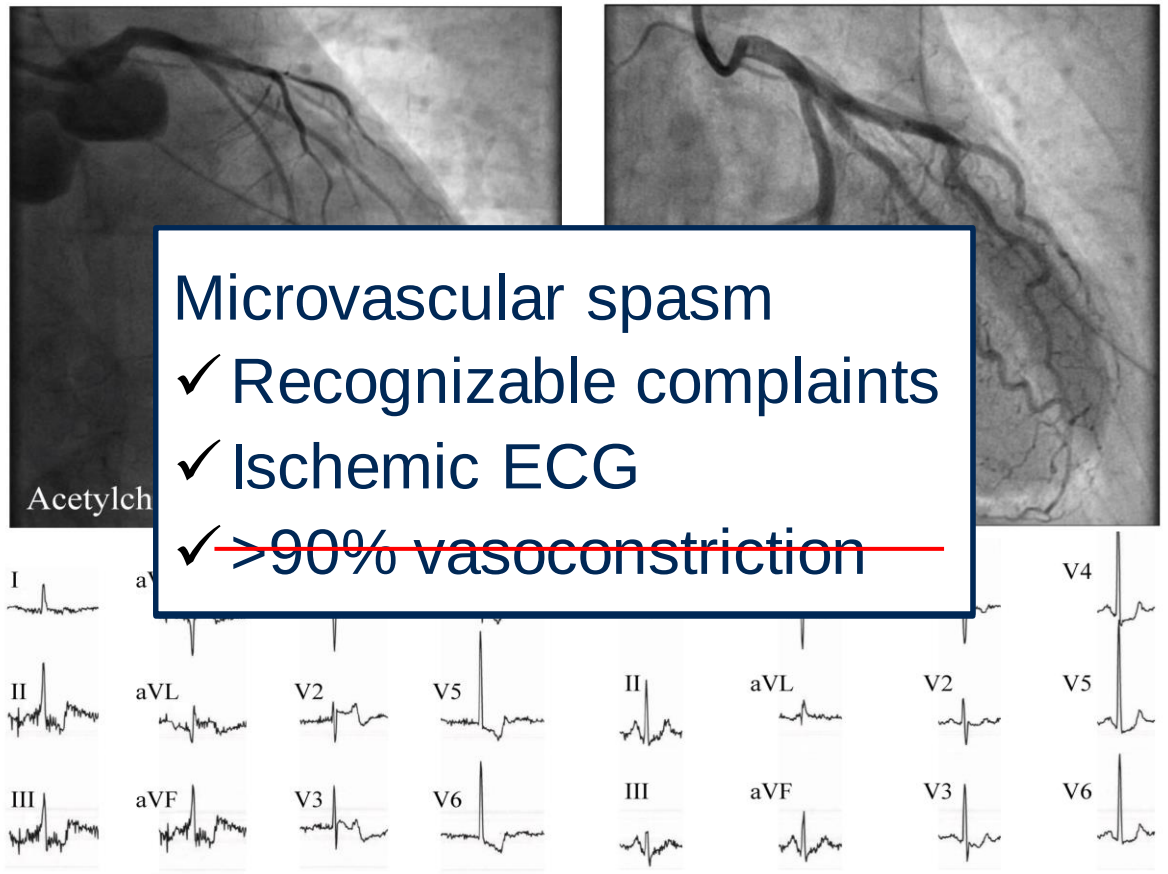
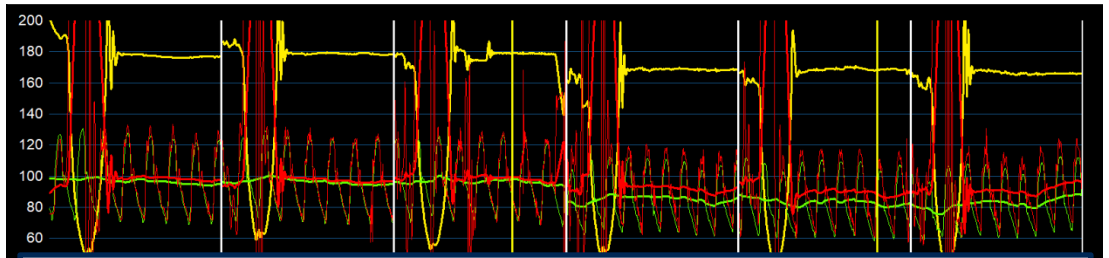
Methods – Coronary function testing

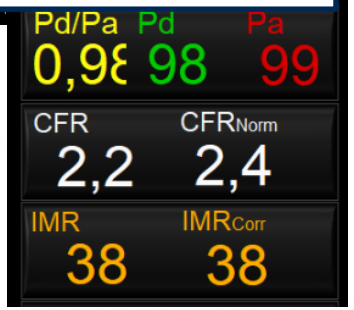
- Endotype
  - Coronary artery spasm
- Method
  - Acetylcholine (ACH) spasm provocation
- Assessment
  - Epicardial spasm
  - Microvascular spasm
  - No spasm



Methods – Coronary function testing

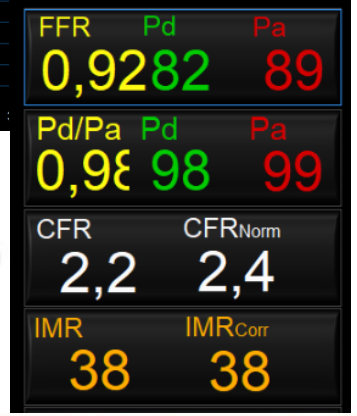


Coronary Microvascular Dysfunction
- CFR < 2.0
and/or
- IMR ≥ 25



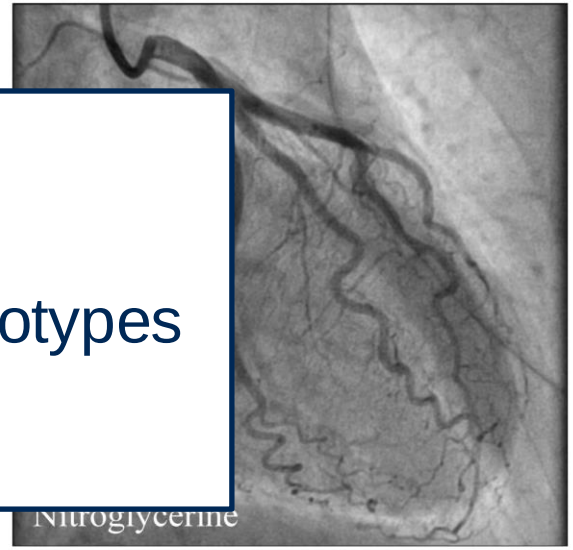
- Endotype
  - Coronary microvascular dysfunction (CMD)
- Method
  - Bolus thermodilution method with adenosine (ADE)
- Assessment
  - Coronary flow reserve (CFR)
  - Index of microvascular resistance (IMR)

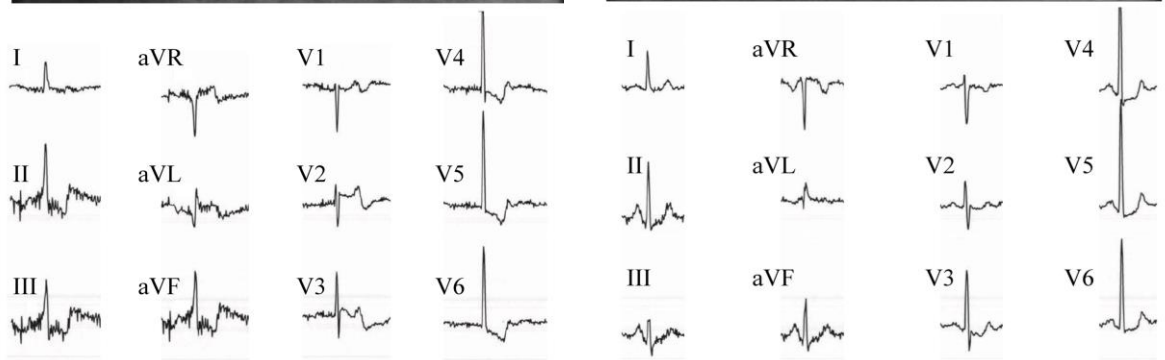
Methods – Primary endpoint



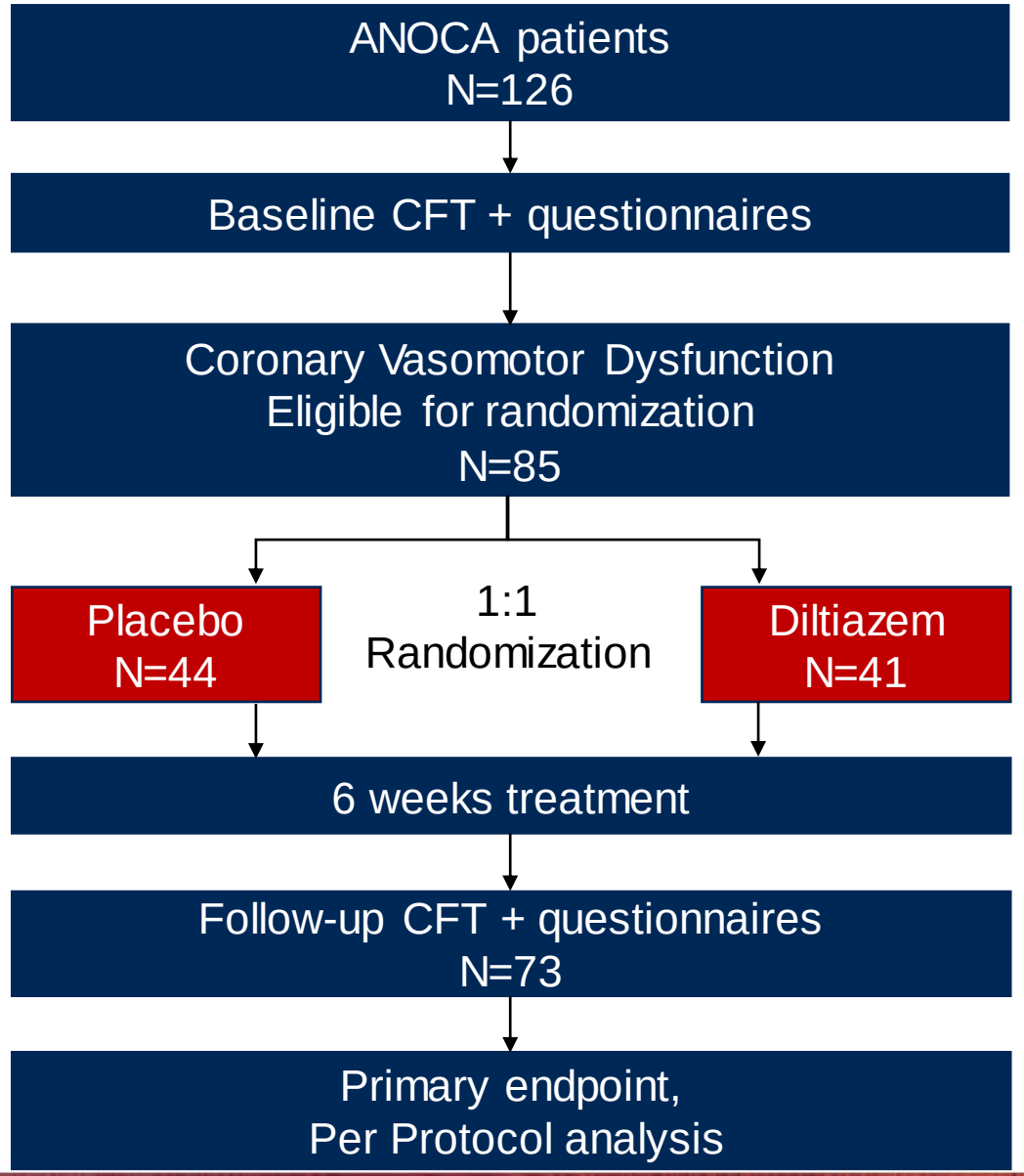
Successful treatment:

- Normalization of one of the abnormal endotypes
- No normal endotype becoming abnormal





Trial flow diagram



Results - Baseline

	Placebo N = 44	Diltiazem N = 41
Age (years)	58 ± 9	58 ± 9
Male gender	36%	31%
History of MI	18%	15%
History of PCI	23%	22%
Hypertension	52%	54%
Dyslipidemia	41%	46%
Diabetes	9%	10%
Current/former smoker	54%	41%
Premature CAD in first-degree relative	52%	51%
Migraine	16%	12%

	Placebo N = 44	Diltiazem N = 41
Angina characteristics		
Angina CCS III/IV	52%	44%
Angina at rest	89%	85%
Angina occurs during exercise	77%	76%
Medication		
Aspirin	46%	54%
Beta-blocker	30%	32%
Statin	34%	54%
ACEi/ARB	39%	44%
Nitrates	23%	27%
Nicorandil	11%	22%

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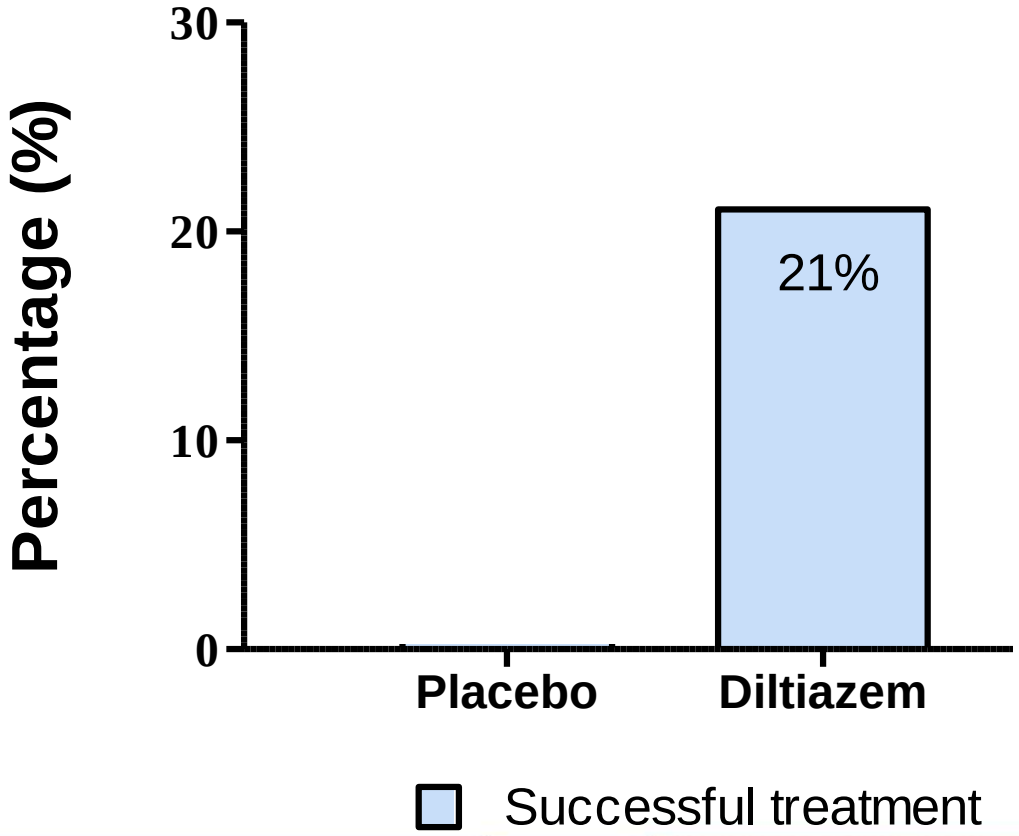
Results – Baseline CFT

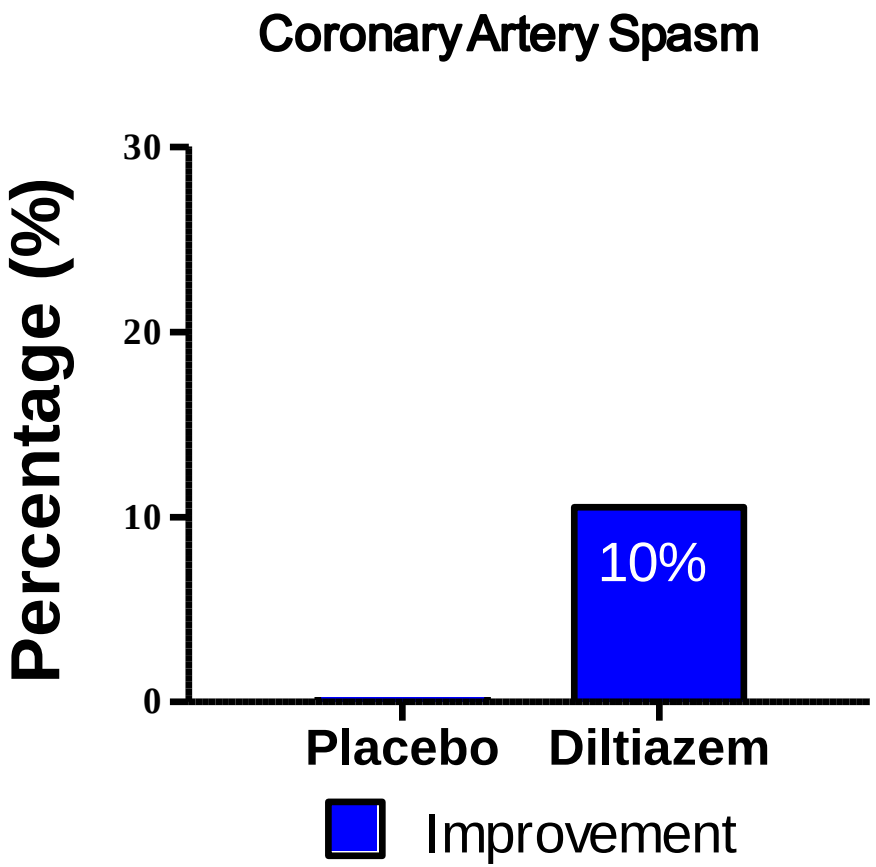
	Placebo N = 44	Diltiazem N = 41
First ACH test		
Epicardial spasm	24 (55%)	19 (48%)
Microvascular spasm	11 (25%)	10 (25%)
No spasm	9 (20%)	11 (27%)
First ADE test		
Microvascular dysfunction	32 (73%)	22 (54%)
Normal function	12 (27%)	19 (46%)

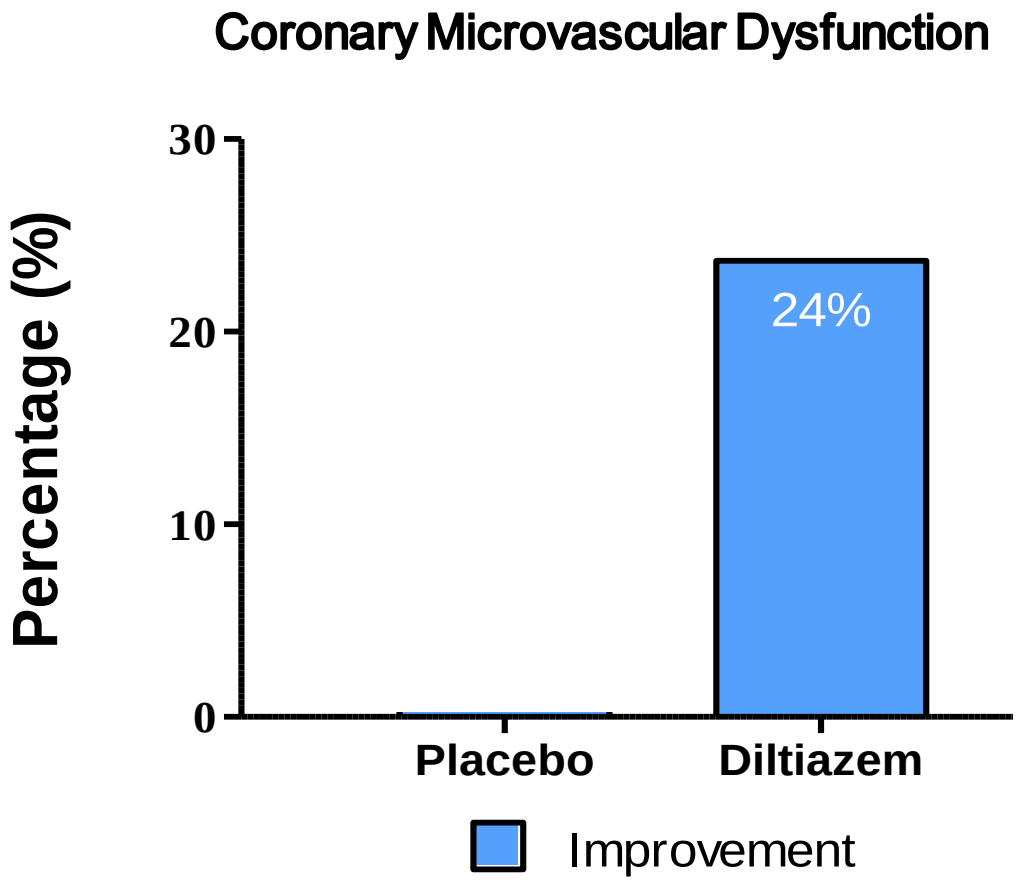
Results – Primary outcome



No difference in treatment success on coronary vasomotor dysfunction

Results – Primary outcome





Results – Secondary outcomes

	Placebo (n = 35)		Diltiazem (n = 38)		Intervention Effect	
	Baseline	Follow-up	Baseline	Follow-up	Difference in Change	P-value
Physiological measurements						
CFR	3.1 ± 1.5	4.1 ± 2.7	3.7 ± 1.6	3.2 ± 1.2	1.35	**0.012**
IMR	27.2 ± 11.7	27.5 ± 19.1	25.3 ± 12.7	23.5 ± 13.6	3.5	0.43
Tmn (rest)	1.04 ± 0.47	1.21 ± 0.54	1.00 ± 0.38	0.95 ± 0.40	0.23	**0.05**
Tmn (hyperemia)	0.36 ± 0.18	0.37 ± 0.25	0.31 ± 0.18	0.32 ± 0.19	0.006	0.92

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CFR increases in placebo and decreases in diltiazem

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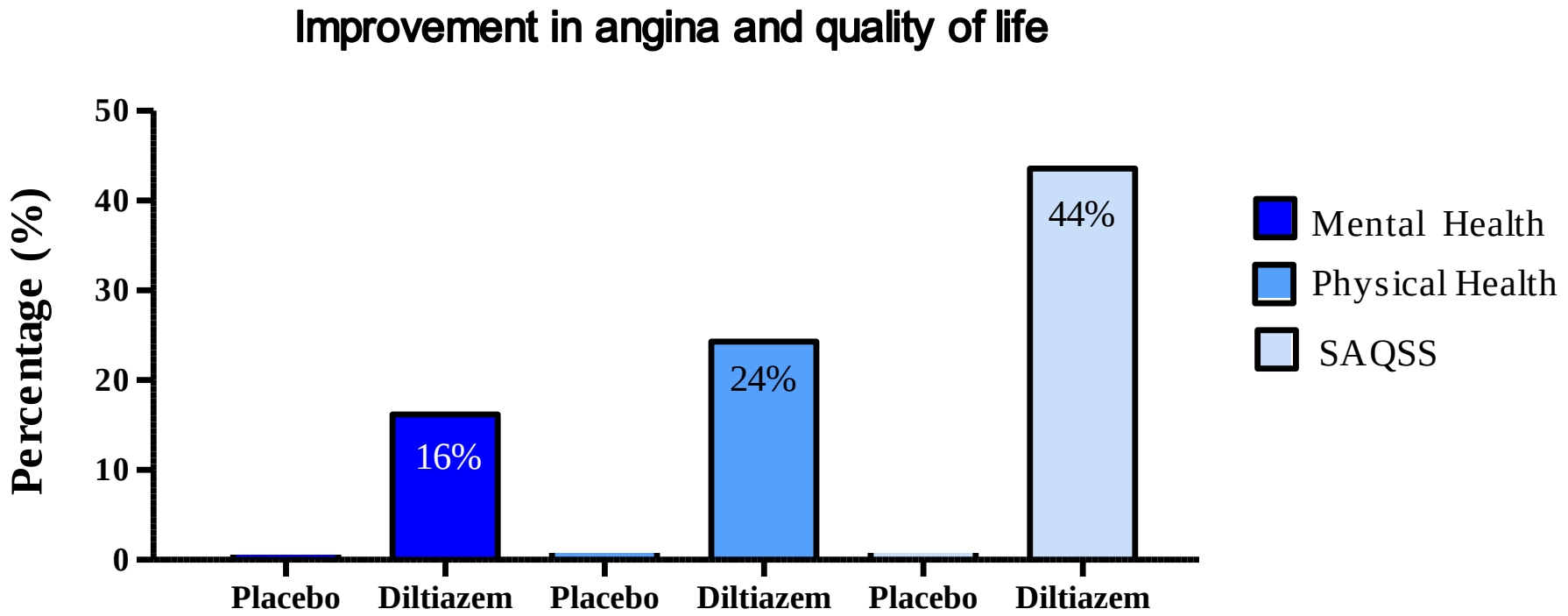
Tmn (hyperemia)	0.36 ± 0.18	0.37 ± 0.25	0.31 ± 0.18	0.32 ± 0.19	0.006	0.92

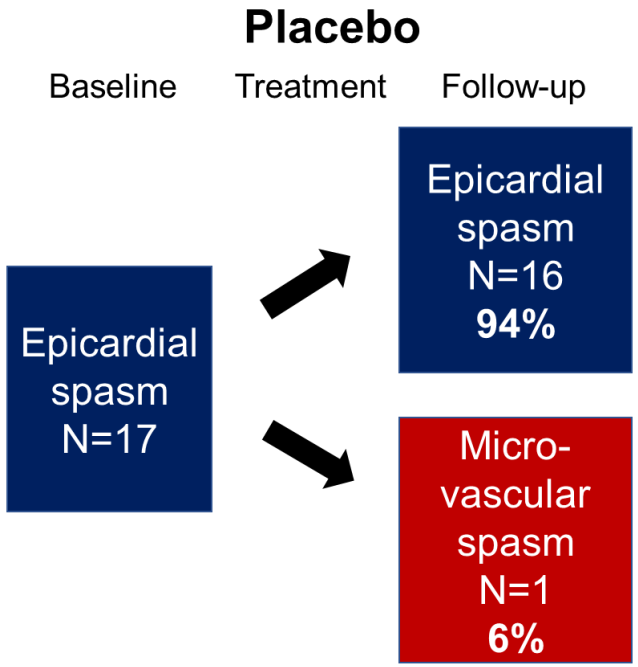
No differences in change in IMR between placebo and diltiazem

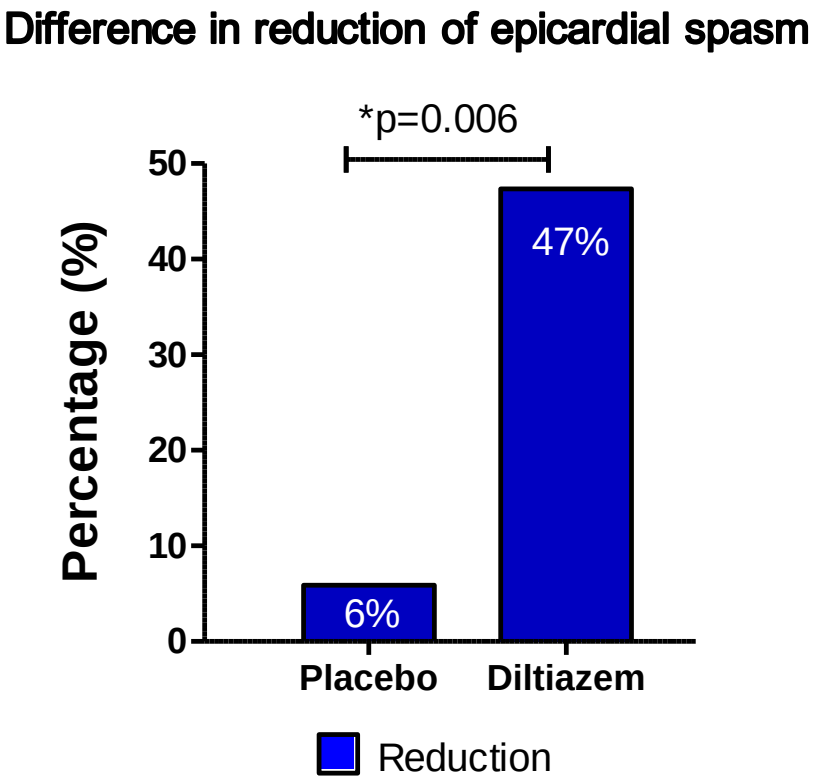
Results – Secondary outcomes



No difference in symptom improvement between placebo and diltiazem

Results – Secondary outcomes





Diltiazem seems to reduce epicardial spasm

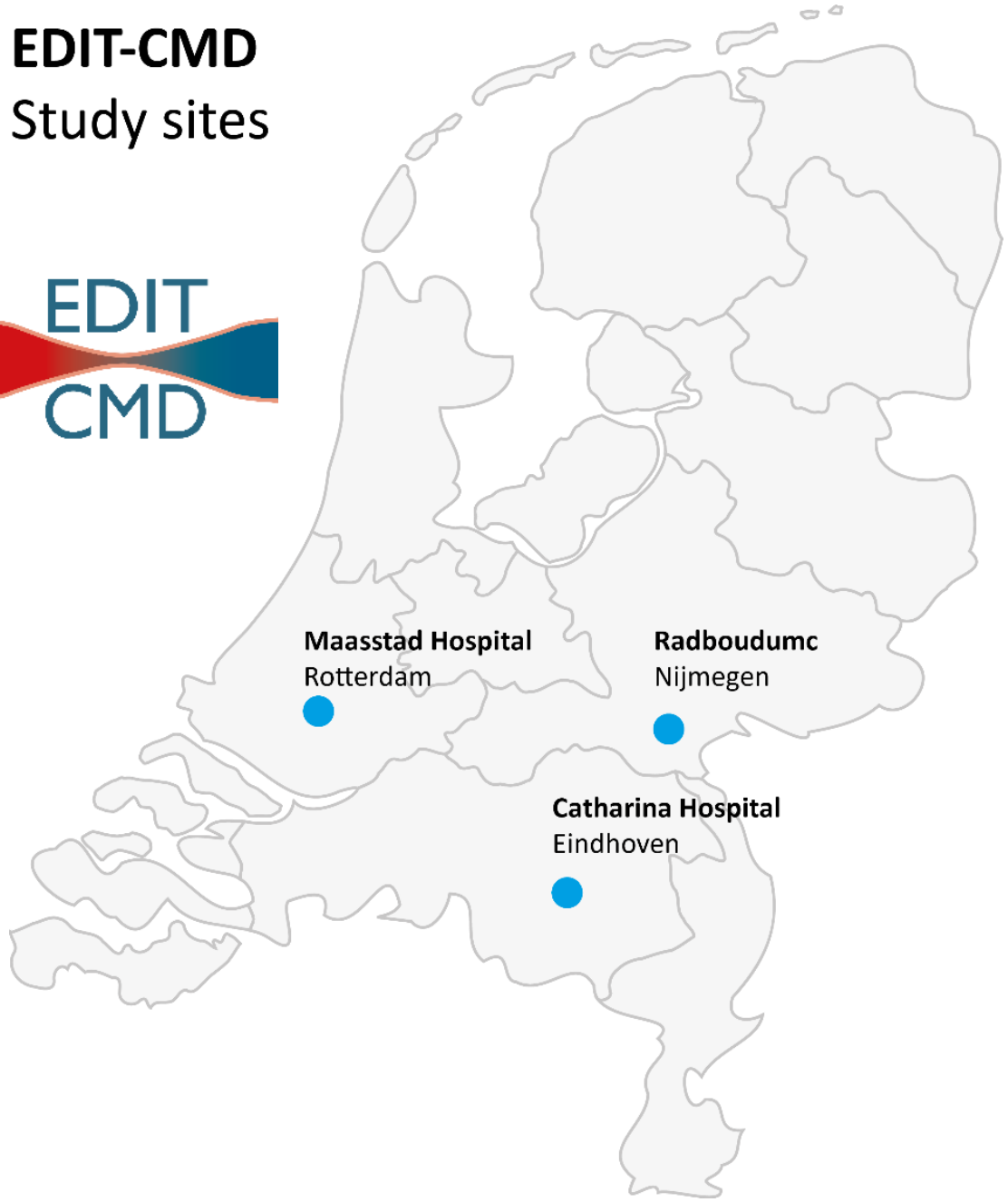
Conclusions

- 6 weeks of treatment with diltiazem was not effective in improving coronary vasomotor dysfunction, symptoms or quality of life as compared to placebo
- Diltiazem seems to reduce epicardial spasm as compared to placebo
- Large trials on the effect of medical therapy on the individual endotypes are warranted
- This study using repeated CFT provides a platform for future research

Publication

- The manuscript of the EDIT-CMD trial is accepted for simultaneous publication in JACC Cardiovascular Imaging

EDIT-CMD
Study sites



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COMPLETE Trial QoL

Effects of Complete Revascularization on Angina-Related Quality of Life in Patients with ST-Segment Elevation Myocardial Infarction

Shamir R. Mehta, Jia Wang, David A. Wood, John A. Spertus, David J. Cohen, Roxana Mehran, Robert F. Storey, Philippe Gabriel Steg, Natalia Pinilla-Escheverri, Tej Sheth, Kevin R. Bainey, Sripal Bangalore, Warren J. Cantor, David P. Faxon, Laurent J. Feldman, Sanjit S. Jolly, Vijay Kunadian, Shahar Lavi, Jose Lopez-Sendon, Mina Madan, Raul Moreno, Sunil V. Rao, Josep Rodés-Cabau, Goran Stanković, Shrikant I. Bangdiwala and John A. Cairns
for the COMPLETE trial Investigators

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE
Hamilton Health Sciences
McMaster University HEALTH SCIENCES

COMPLETE TRIAL

Disclosures

The COMPLETE Trial was funded by the Canadian Institutes of Health Research and the Population Health Research Institute with additional unrestricted grants from AstraZeneca and Boston Scientific.

Coordinated by the Population Health Research Institute, Hamilton, Canada

COMPLETE TRIAL

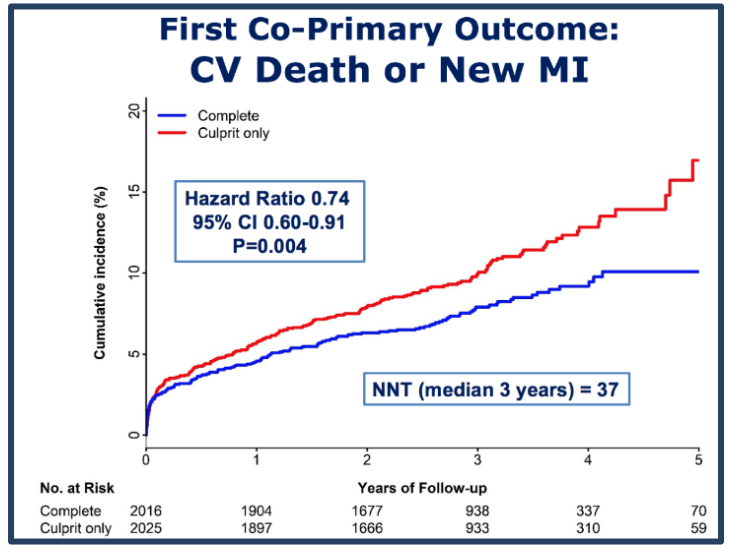
Background

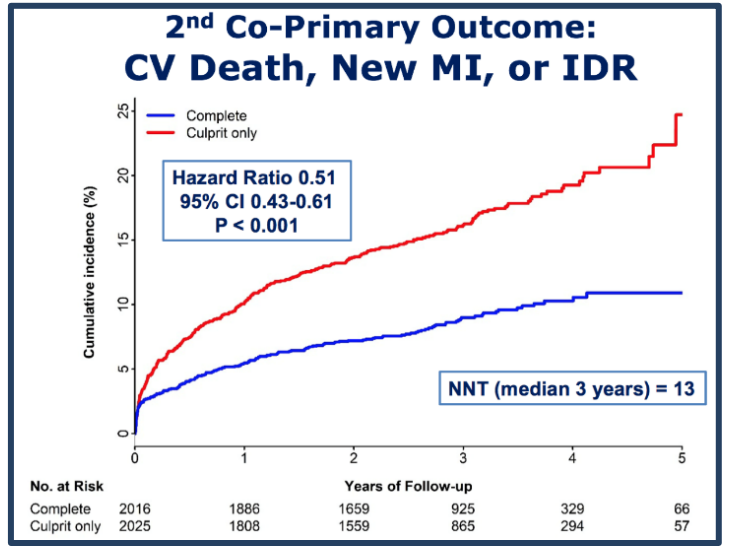
- The goals of treatment in patients with STEMI and multivessel CAD are to reduce major cardiovascular events AND improve quality of life

- The COMPLETE trial demonstrated that complete revascularization reduced CV death or new MI and this led to a Class 1A recommendation for complete revascularization in the 2021 ACC/AHA/AATS/STS/SCAI Guideline for Coronary Artery Revascularization[2]

- ***However, the effect of complete revascularization on angina-related quality of life is uncertain and*** *has not previously been evaluated in a RCT*

COMPLETE Trial Main Results





1. Mehta SR et al. N Engl J Med 2019; 381, 1411-1421
2. Lawton JS et al. J Am Coll Cardiol. 2022;79:e21-e129

COMPLETE TRIAL

Primary Objective

To determine whether complete revascularization improves angina-related quality of life compared with culprit-lesion only PCI in patients with STEMI and multivessel CAD.

COMPLETE TRIAL

SAQ, Outcomes and Analysis

- Pre-specified analysis of the COMPLETE trial*
- Seattle Angina Questionnaire was administered at baseline (randomization), 6 months and final visit (median 3 years).
- SAQ is a a 19-item questionnaire completed by the patient that assesses frequency of angina, treatment satisfaction, angina stability, physical limitation, and quality of life.
- Scores range from 0 to 100 for each domain with higher scores indicating better health status and fewer symptoms.
- **Main outcomes:** SAQ-AF score as a continuous variable and SAQ-AF score=100 (proportion free of angina)
- **Analysis:** Intention-to-treat, mixed model repeated measures analysis (MMRM) for SAQ and GLMM for proportion angina-free

*Mehta SR et al. *Am Heart J* 2019; 215:157-166.

COMPLETE QoL Design

STEMI WITH MULTIVESSEL CAD AND SUCCESSFUL PCI TO THE CULPRIT LESION

MVD defined as at least one additional non-culprit lesion ≥ 2.5 mm diameter and ≥70% stenosis or 50-69% with FFR ≤0.80

Randomized to COMPLETE REVASCULARIZATION (Staged Non-Culprit Lesion PCI plus Optimal Medical Therapy)

n=2016

Received Allocated Intervention (n=1881)

Did not receive Allocated Intervention (n=135)

- Crossover to Culprit Lesion-Only Revascularization (n=122)
- Death prior to intervention (n=13)

Lost to Follow-up (n=18)

Withdrew Consent (n=3)

SAQ FREQUENCY SCORE Completed/Expected

Baseline: n=1905/2016 (94.5%)

Month 6: n=1734/1981 (87.5%)

End of study: n=1666/1920 (86.8%)

Randomized to CULPRIT LESION-ONLY REVASCULARIZATION (Optimal Medical Therapy Only)

n=2025

Received Allocated Intervention (n=1634)

Did not receive Allocated Intervention (n=391)

- Met protocol criteria for Complete Revascularization (n=198)
- Did not meet protocol criteria for Complete Revascularization (n=193)

Lost to Follow-up (n=15)

Withdrew Consent (n=6)

SAQ FREQUENCY SCORE Completed/Expected

Baseline: n=1925/2025 (95.1%)

Month 6: n=1730/1995 (86.7%)

End of study: n=1632/1919 (85.0%)

MEDIAN FOLLOW-UP: 3 YEARS

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Hamilton Health Sciences

McMaster University HEALTH SCIENCES

COMPLETE TRIAL

Baseline Clinical Characteristics and SAQ Score

	Complete N=2016	Culprit-only N=2025
Age (yrs)	61.6	62.4
Gender (% male)	80.5	79.1
Diabetes (%)	19.1	19.9
Chronic renal insuff. (%)	2.0	2.3
Prior MI (%)	7.3	7.6
Current smoker (%)	40.6	38.9
Hypertension (%)	48.7	50.7
Dyslipidemia (%)	37.9	39.4
Prior PCI (%)	7.0	7.0
Prior stroke (%)	3.2	3.1

	Complete N=2016	Culprit-only N=2025
SAQ score		
Angina frequency	87.1±17.8	87.2±18.4
Daily	34/1905 (1.8)	39/1925 (2.0)
Weekly	211/1905 (11.1)	211/1925 (11.0)
Monthly	719/1905 (37.7)	675/1925 (35.1)
None	941/1905 (49.4)	1000/1925 (51.9)
Physical limitation	84.9±20.4	84.4±20.8
Treatment satisfaction	93.0±12.4	92.5±12.5
Quality of life	66.9±23.0	66.3±23.5
Summary score*	79.6±15.7	79.3±16.7

COMPLETE TRIAL

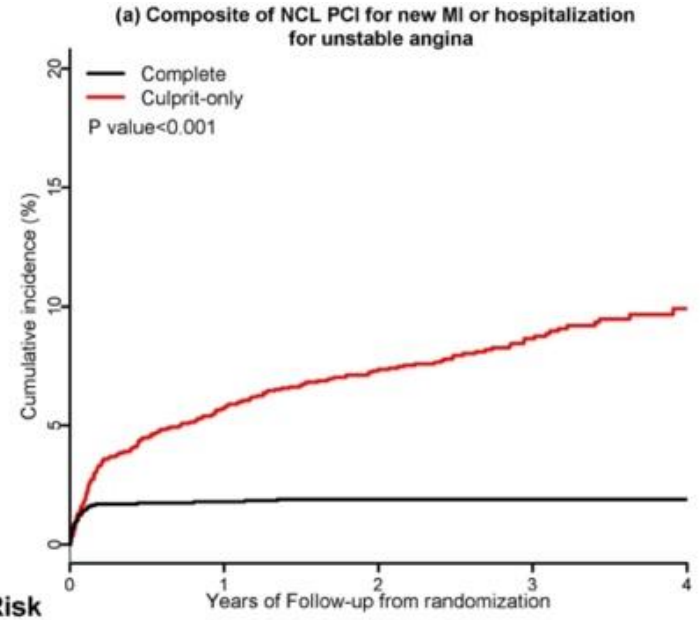
Baseline Clinical Characteristics and SAQ Score

	Complete N=2016	Culprit-only N=2025
Age (yrs)	61.6	62.4
Gender (% male)	80.5	79.1
Diabetes (%)	19.1	19.9
Chronic renal insuff. (%)	2.0	2.3
Prior MI (%)	7.3	7.6
Current smoker (%)	40.6	38.9
Hypertension (%)	48.7	50.7
Dyslipidemia (%)	37.9	39.4
Prior PCI (%)	7.0	7.0
Prior stroke (%)	3.2	3.1

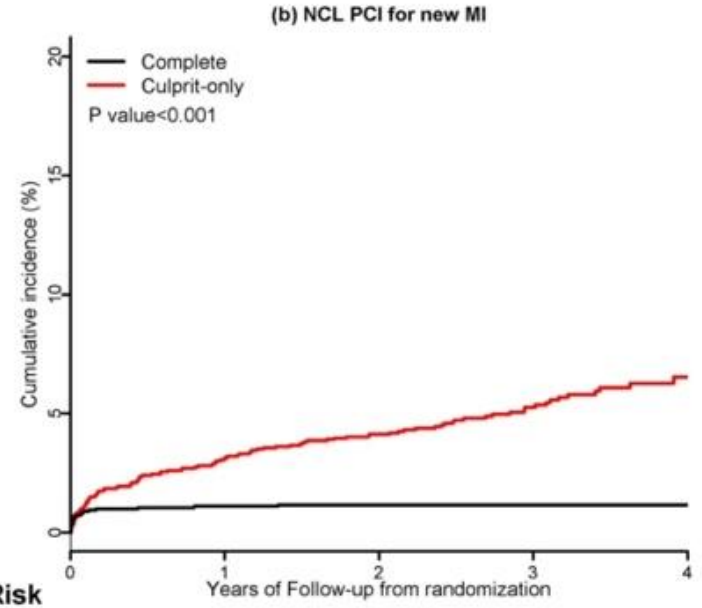
	Complete N=2016	Culprit-only N=2025
SAQ score		
Angina frequency	87.1±17.8	87.2±18.4
Daily	34/1905 (1.8)	39/1925 (2.0)
Weekly	211/1905 (11.1)	211/1925 (11.0)
Monthly	719/1905 (37.7)	675/1925 (35.1)
None	941/1905 (49.4)	1000/1925 (51.9)
Physical limitation	84.9±20.4	84.4±20.8
Treatment satisfaction	93.0±12.4	92.5±12.5
Quality of life	66.9±23.0	66.3±23.5
Summary score*	79.6±15.7	79.3±16.7

COMPLETE TRIAL

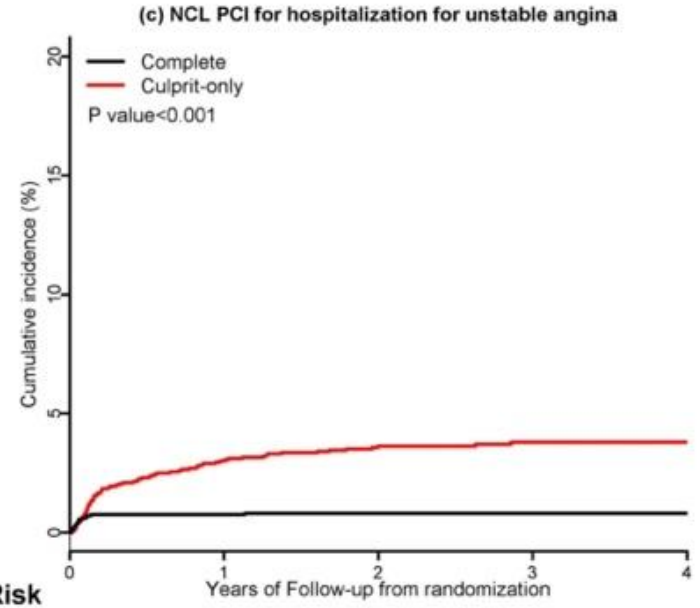
Crossover PCI of Non-culprit Lesion after Angina-Related Clinical Event



No. at Risk					
Complete	2016	1926	1713	968	344
Culprit-only	2025	1865	1637	917	311



No. at Risk					
Complete	2016	1940	1725	976	351
Culprit-only	2025	1917	1694	954	321



No. at Risk					
Complete	2016	1945	1732	984	349
Culprit-only	2025	1918	1699	964	329

COMPLETE TRIAL

SAQ Subscale Scores at Follow-up (6 months)

SAQ Subscale	Score at Follow-up		Δ from Baseline		Difference (95% CI)	P Value
	Complete	Culprit	Complete	Culprit		
Angina frequency	94.6±13.0	93.6±14.7	7.3±20.2	6.4±21.6	0.96 (0.05-1.88)	0.039
Physical limitation	88.8±17.7	88.0±18.0	3.3±19.7	3.3±21.1	0.83 (-0.39-2.04)	0.18
Treatment satisfaction	93.7±11.1	92.2±12.7	0.7±13.8	-0.2±15.0	1.44 (0.65-2.23)	<0.001
Quality of life score	80.4±18.9	78.0±20.7	13.2±24.0	11.5±27.0	2.26 (0.94-3.58)	<0.001
Summary score	80.4±18.9	78.0±20.7	13.2±24.0	11.5±27.0	2.26 (0.94-3.58)	<0.001

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SAQ Subscale Scores at Follow-up (Median 3 Years)

SAQ Subscale	Score at Follow-up		Δ from Baseline		Difference (95% CI)	P Value
	Complete	Culprit	Complete	Culprit		
Angina frequency	97.1±9.7	96.3±10.9	9.8±18.9	8.6±19.9	0.97 (0.27-1.67)	0.006
Physical limitation	91.1±15.7	89.9±17.4	4.2±20.0	4.3±22.3	1.41 (0.24-2.59)	0.018
Treatment satisfaction	93.3±12.4	92.5±13.2	0.6±15.1	0.2±16.2	0.97 (0.10-1.84)	0.028
Quality of life score	83.6±18.0	82.5±18.4	16.3±25.6	15.9±27.2	1.25 (0.01-2.48)	0.048
Summary score	90.7±11.4	89.5±12.2	9.8±15.8	9.6±18.0	1.27 (0.44-2.11)	0.003

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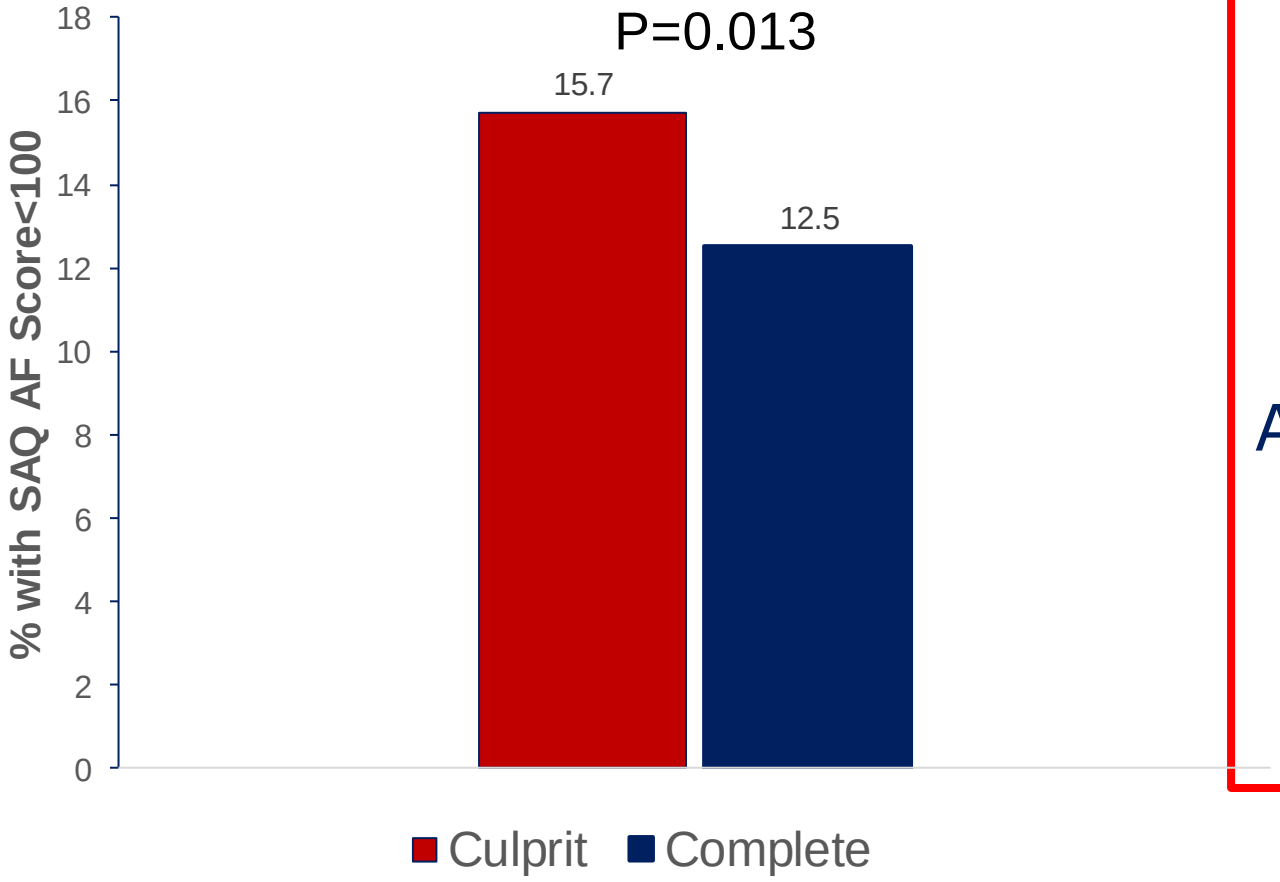
Angina Status at Study End

Residual Angina

Absolute Difference 3.21%
P=0.013



Proportion Angina Free

(SAQ-AF Score=100)

87.5% Complete Revasc
vs
84.3% Culprit-Lesion-only

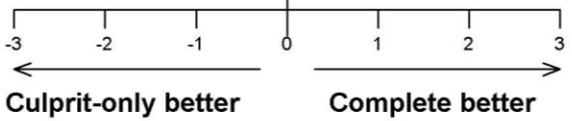
ARD=3.2% 95% CI 0.7-5.7%

Number Needed to Treat=31

P=0.013

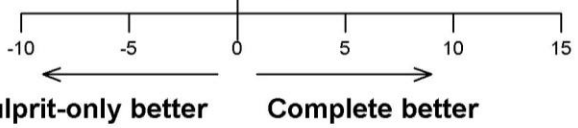
Pre-Defined Subgroups (SAQ-AF Score)

Subgroup	Score at 3 years				Change from baseline				Absolute difference (95% CI)	P value for interaction
	Complete		Culprit-only		Complete		Culprit-only			
	N	*mean±SD*	*N*	*mean±SD*	*N*	*mean±SD*	*N*	*mean±SD*		
Overall	1666	97.1±9.7	1632	96.3±10.9	1587	9.8±18.9	1572	8.6±19.9	0.97 (0.27-1.67)	
Intent to perform non-culprit lesion PCI										0.80
During initial hospitalization	1132	97.5±8.7	1120	96.7±10.4	1072	10.0±18.7	1074	9.2±19.9	0.91 (0.07-1.76)	
After initial hospitalization	534	96.4±11.4	512	95.4±11.8	515	9.2±19.5	498	7.3±19.7	1.11 (-0.13-2.35)	
Proximal/mid LAD non-culprit stenosis										0.86
Presence	700	97.2±9.9	686	96.1±11.2	670	9.0±18.5	663	8.7±20.0	1.03 (-0.05-2.11)	
Absence	894	97.3±9.3	882	96.3±10.8	853	10.2±18.8	846	8.5±20.1	1.16 (0.21-2.11)	
Non-culprit stenosis severity ≥ 80% visual or ≥ 60% core lab										0.05
Presence	1379	97.2±9.6	1313	96.0±11.1	1311	9.7±18.6	1267	8.9±20.5	1.29 (0.51-2.06)	
Absence	285	96.8±10.4	318	97.5±9.6	274	9.9±20.4	304	7.4±16.9	-0.50 (-2.14-1.13)	
Residual SYNTAX score										0.10
<6(median)	730	97.3±9.1	710	96.9±9.6	693	10.1±18.4	682	8.4±19.0	0.44 (-0.62-1.49)	
≥ 6(median)	865	97.2±9.9	863	95.7±11.9	831	9.3±18.9	831	8.7±20.8	1.63 (0.67-2.60)	
Angina frequency at baseline										0.88
Daily/weekly	203	94.0±15.4	193	93.5±14.4	203	43.4±21.3	193	44.6±21.1	0.64 (-1.38-2.67)	
Monthly	598	96.7±10.2	563	95.6±12.1	598	13.6±12.2	563	12.7±13.7	1.21 (0.02-2.39)	
None	786	98.1±7.4	816	97.3±8.9	786	-1.9±7.4	816	-2.7±8.9	0.93 (-0.08-1.94)	



Pre-Defined Subgroups (Angina-Free at 3 Years)

Subgroup	Complete	Culprit-only	Difference in proportions (%) with 95% CI	P value for Interaction
	no. of events/total no. (%)			
Overall	1457/1666 (87.5)	1376/1632 (84.3)	3.21 (0.69-5.73)	
Intent to perform non-culprit lesion PCI				0.16
During initial hospitalization	997/1132 (88.1)	967/1120 (86.3)	1.73 (-1.02-4.49)	
After initial hospitalization	460/534 (86.1)	409/512 (79.9)	6.26 (1.72-10.80)	
Proximal/mid LAD non-culprit stenosis				0.97
Presence	616/700 (88.0)	577/686 (84.1)	3.90 (0.13-7.67)	
Absence	789/894 (88.3)	747/882 (84.7)	3.96 (0.61-7.30)	
Non-culprit stenosis severity ≥ 80% visual or ≥ 60% core lab				0.017
Presence	1210/1379 (87.7)	1093/1313 (83.2)	4.71 (1.95-7.48)	
Absence	245/285 (86.0)	283/318 (89.0)	-3.16 (-8.69-2.37)	
Residual SYNTAX score				0.09
<6(median)	641/730 (87.8)	615/710 (86.6)	1.32 (-2.28-4.92)	
≥ 6(median)	765/865 (88.4)	714/863 (82.7)	6.01 (2.56-9.45)	
Angina frequency at baseline				0.96
Daily/weekly	167/203 (82.3)	149/193 (77.2)	5.55 (-2.66-13.76)	
Monthly	508/598 (84.9)	454/563 (80.6)	4.32 (-0.16-8.79)	
None	710/786 (90.3)	718/816 (88.0)	2.52 (-0.65-5.70)	



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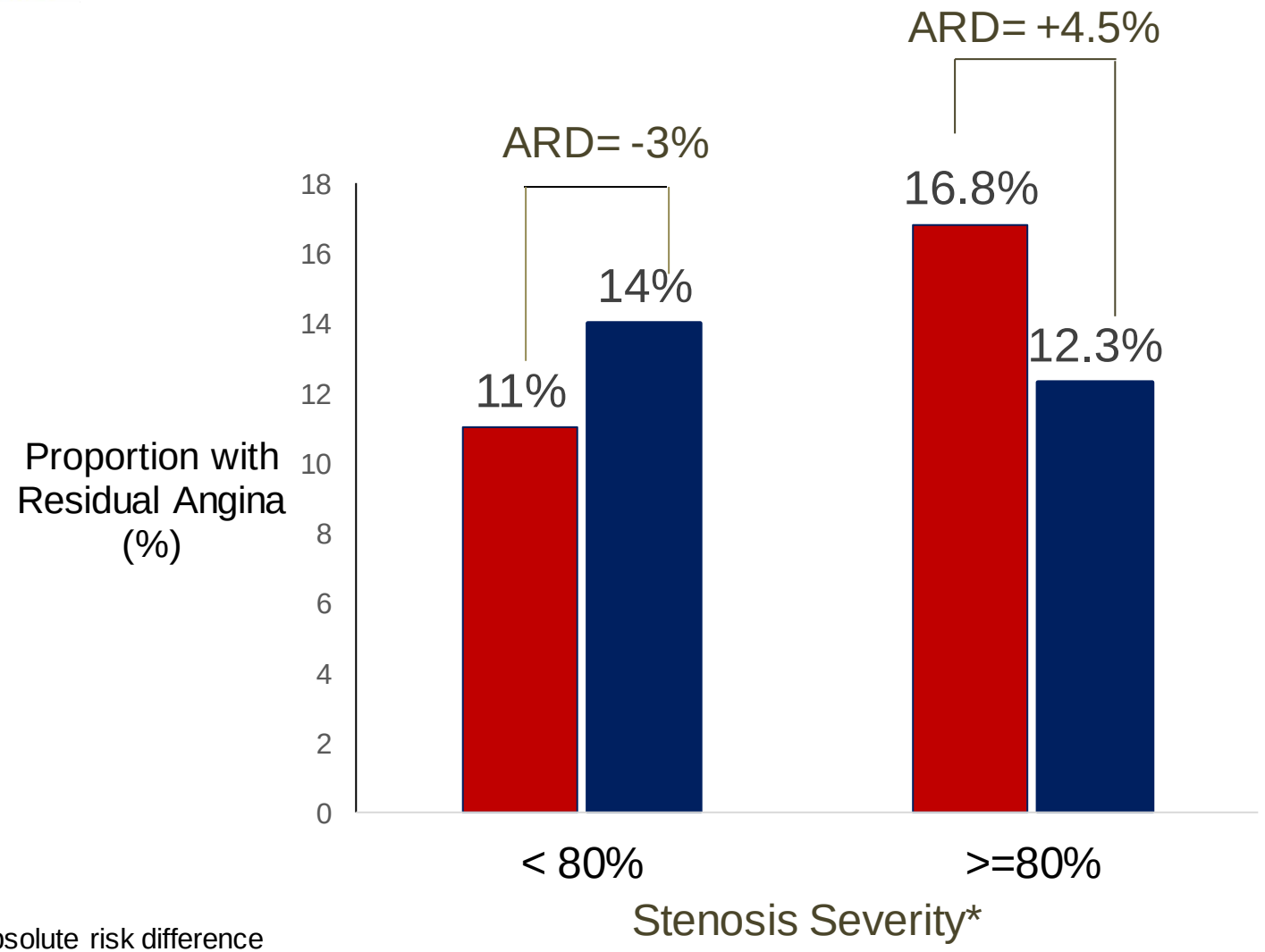
Residual Angina at Study End (Median 3 Years) According to Non-Culprit Lesion Stenosis Severity



Interaction P =0.017

Culprit-Lesion-only

Complete Revascularization

ARD=absolute risk difference

*Visual estimation or 60% by QCA (angiographic core lab)

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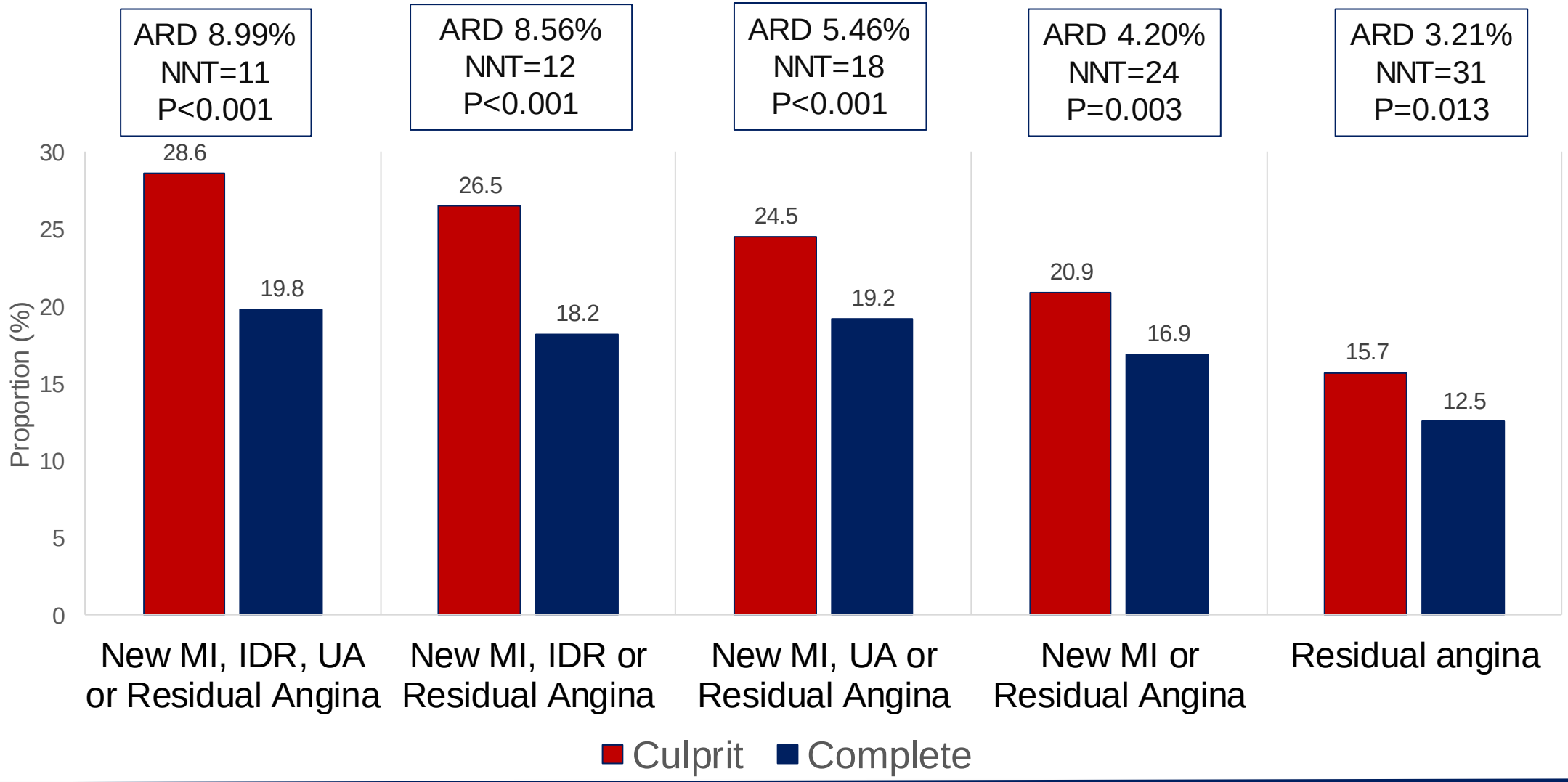
Total Angina Burden
Randomization to Follow-up



Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

ARD=absolute risk difference, NNT=number needed to treat, IDR=ischemia-driven revascularization, UA=unstable angina

Hamilton Health Sciences
McMaster University HEALTH SCIENCES

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Limitations

1. 14% of health status measurements were missing at final follow-up. Sensitivity analyses, including multiple imputation were consistent with the primary results

2. SAQ measured at only 3 timepoints. More interim assessments would have allowed for a more granular assessment of angina status in the intervening time periods.

3. Approximately 13% of patients crossed over from culprit-lesion only PCI to complete revascularization after experiencing an angina-related outcome event (MI, ischemia-driven revascularization or unstable angina), which may have narrowed the difference in angina status at study end as measured by the SAQ.

To address #2 and #3, we evaluated total angina burden, which included not only residual angina at study end, but also any angina-associated events over the course of the trial, and this demonstrated a consistent benefit of complete revascularization.

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Conclusions

In Patients with STEMI and MVD:

- Both a complete revascularization and a culprit-lesion-only strategy resulted in substantial improvements in overall angina-related quality of life compared with baseline.
- At a median follow-up of 3 years, a greater proportion of patients were free of angina in the complete revascularization group than in the culprit-lesion-only group, translating into a number needed to treat of 31 patients to prevent one patient from experiencing angina at a median follow-up of 3 years.

- The benefit of CR was observed entirely in patients with NCL stenosis severity ≥80%.
- This difference is notable given crossover to NCL PCI in the culprit lesion only group after an angina-related ischemic event
- Total angina burden from randomization to follow-up (including all angina-related events and residual angina at study end) was substantially reduced with complete revascularization

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Implications

- Complete revascularization improves overall patient-reported health status in addition to its established benefit in reducing major cardiovascular events

- These data also provide important new information for physicians to consider in the context of shared decision making as it relates to coronary artery revascularization in patients with STEMI.

COMPLETE TRIAL

Acknowledgments

COMPLETE QoL Sub-Committee

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We thank all investigators, study coordinators and participants

POISE-3

PeriOperative ISchemic Evaluation-3 Trial

Hypotension-avoidance strategy versus hypertension-avoidance strategy in patients undergoing noncardiac surgery

Maura Marcucci on behalf of POISE-3 Investigators

McMaster University, Population Health Research Institute, Hamilton, ON, Canada

Funding: Canadian Institutes of Health Research (Canada), National Health and Medical Research Council (Australia), Research Grant Council (Hong Kong SAR)

Background

- >300 millions/year adult noncardiac surgeries
- Major vascular complications frequent
- Hemodynamics abnormalities frequent
  - >25% intraoperative and/or postoperative hypotension
  - linked to major vascular complications
- >50% take chronic antihypertensive medications
  - commonly continued perioperatively (although practice varies)

Rationale

- Small studies with methodological limitations suggest
  - withholding ACEIs/ARBs may reduce perioperative hypotension and vascular complications
  - withholding beta-blockers may increase perioperative vascular complications
- Intraoperative mean arterial pressure (MAP) targets ≥60 mm Hg are commonly used
  - however, based on observational data, it has been questioned whether MAP targets ≥80 mm Hg would improve outcomes

Uncertainty remains regarding optimal perioperative blood pressure management

Research question

- In patients undergoing noncardiac surgery who are at risk of vascular events
  - what are effects of perioperative hypotension-avoidance strategy versus hypertension-avoidance strategy on
    - 30-day incidence of major vascular complications?

Design

- 10,000 patients in tranexamic acid or placebo trial
- Partial 2x2 factorial design
- Expected 6,500 patients in blood pressure trial
- Patients, healthcare providers, and study personnel aware of blood pressure treatment assignment
- Outcome adjudicators masked to treatment assignment

Eligibility criteria

- Included patients
  - ≥45 years old, undergoing inpatient noncardiac surgery
  - at risk of perioperative cardiovascular events
  - chronically taking ≥1 antihypertensive medication
- Excluded patients
  - NYHA class III-IV, or LVEF ≤30%

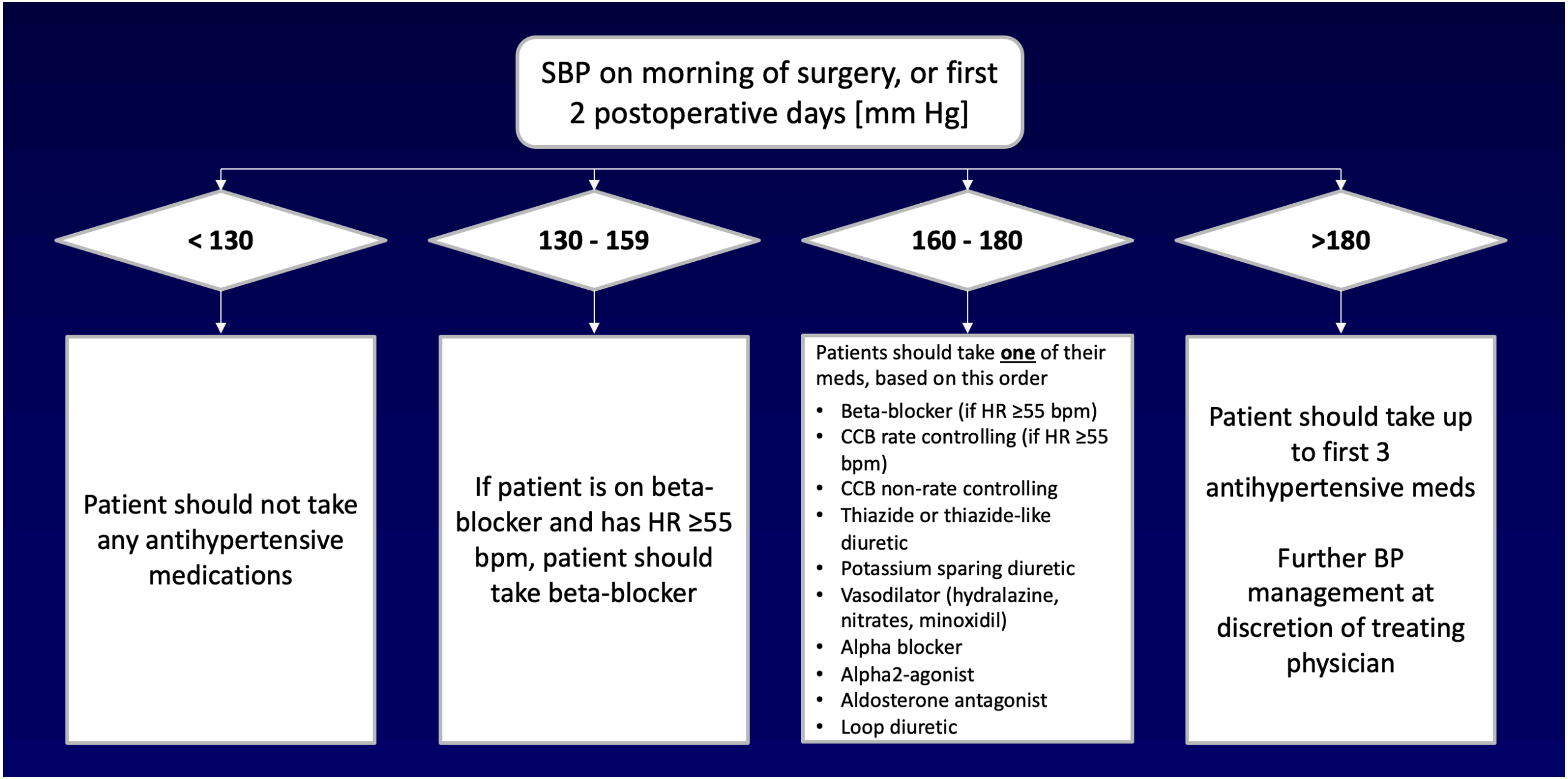
Intervention

- Patients told not to take antihypertensive medications night before and morning of surgery
  - bring medications to preoperative holding area
- hypotension-avoidance vs hypertension-avoidance
  - based on blood pressure abnormality preferentially intended to avoid

Hypotension-avoidance strategy

- Preoperative management
  - hold chronic ACEI/ARBs
  - other chronic antihypertensive meds based on algorithm
- Intraoperative management
  - target MAP ≥80 mm Hg
- Postoperative management for first 2 days after surgery
  - hold chronic ACEI/ARBs
  - other chronic antihypertensive meds based on algorithm

Hypotension-avoidance algorithm



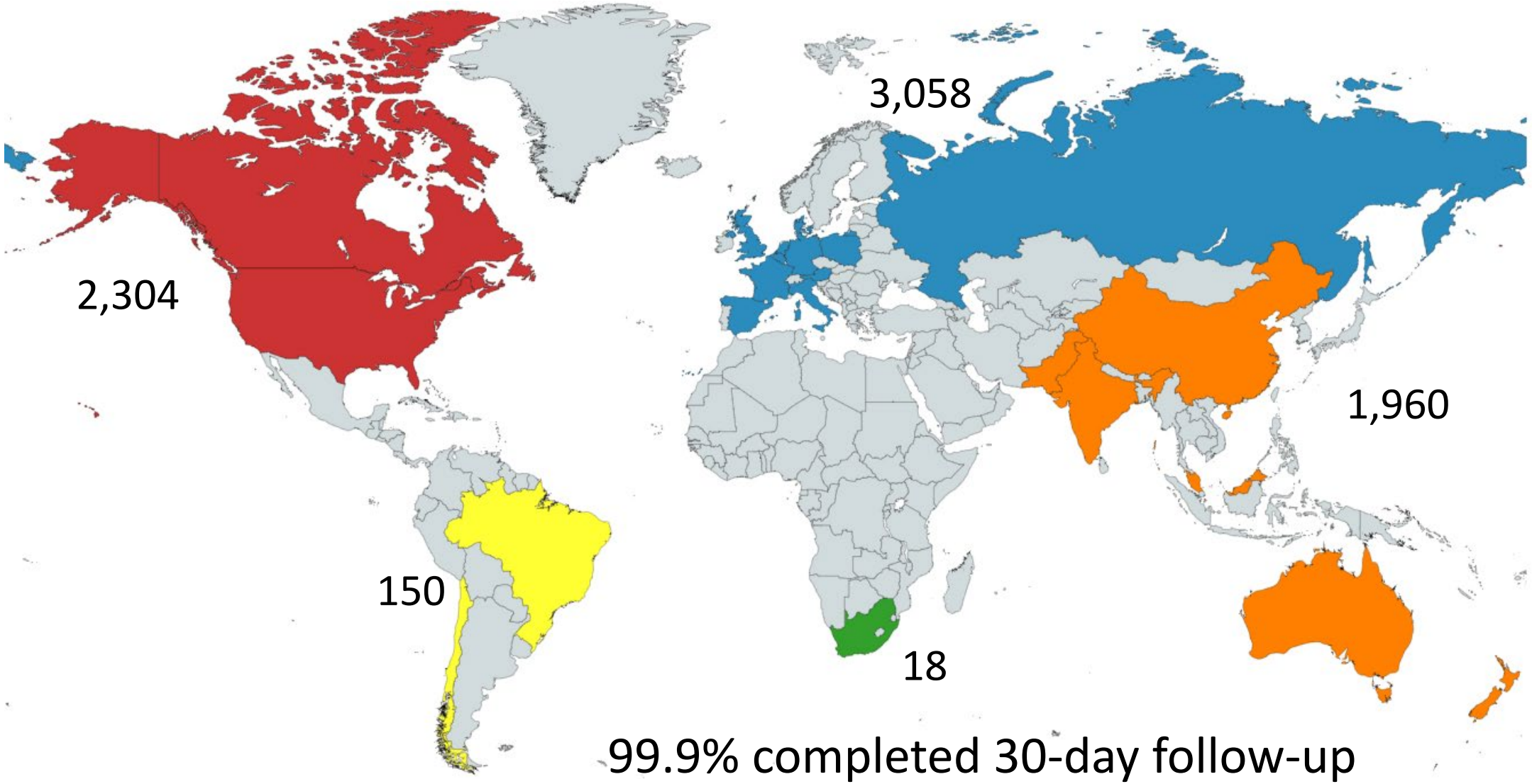
Hypertension-avoidance strategy

- Preoperative management
  - given chronic antihypertensive medications
- Intraoperative management
  - target MAP ≥60 mm Hg
- Postoperative management
  - restart chronic antihypertensive medications after surgery

Primary outcome

- Major vascular complication
  - composite of vascular death and nonfatal myocardial injury after noncardiac surgery (MINS), stroke, and cardiac arrest at 30 days after randomization

7490 patients randomized
110 centres, 22 countries



99.9% completed 30-day follow-up

Baseline characteristics

	Hypotension-avoidance (N = 3742)	Hypertension-avoidance (N = 3748)
age, years	70	70
male	2075 (56%)	2096 (56%)
number of chronic antihypertensive meds		
mean (sd)	2 (1)	2 (1)
≥3 meds	1038 (28%)	1011 (27%)
chronic ACEI or ARB	2684 (72%)	2684 (72%)
chronic beta-blocker	1668 (45%)	1601 (43%)

Intraoperative compliance

	Hypotension-avoidance (N = 3742)	Hypertension-avoidance (N = 3748)	Median difference (95% CI)
Intraoperative MAPs	**Minutes, median (IRQ)***		
MAP <60	0 (0 - 0)	0 (0 - 2)	NA
MAP 60-79	25 (5 - 63)	56 (20 - 108)	-31 (-34 to -28)
MAP ≥80	101 (55 - 165)	70 (26 - 125)	31 (27 to 36)

*mean duration of surgery 170 minutes

Pre- and postoperative compliance

	Hypotension-avoidance (N = 3742)	Hypertension-avoidance (N = 3748)
Day	**% compliance (95% CI)**	
Day of Surgery*	68 (67 - 70)	57 (55 - 58)
Postoperative day 1	75 (73 - 76)	67 (65 - 68)
Postoperative day 2	72 (71 - 74)	70 (69 - 72)

*before and after surgery

Medications received perioperatively

	Day of surgery		Day 1 after surgery		Day 2 after surgery	
	Hypo	**Hyper**	**Hypo**	**Hyper**	**Hypo**	**Hyper**
received ACEI/ARB	5%	38%	6%	47%	7%	50%
received beta-blocker	23%	32%	25%	36%	28%	37%
received ≥1 antihypertensive	36%	70%	39%	79%	42%	83%

Hypo = hypotension-avoidance
Hyper = hypertension-avoidance

Primary outcome

	Hypotension-avoidance N = 3742 n (%)	Hypertension-avoidance N = 3748 n (%)	Hazard ratio (95% CI)	P value
Major vascular complication	520 (13.9)	524 (14.0)	0.99 (0.88-1.12)	0.92

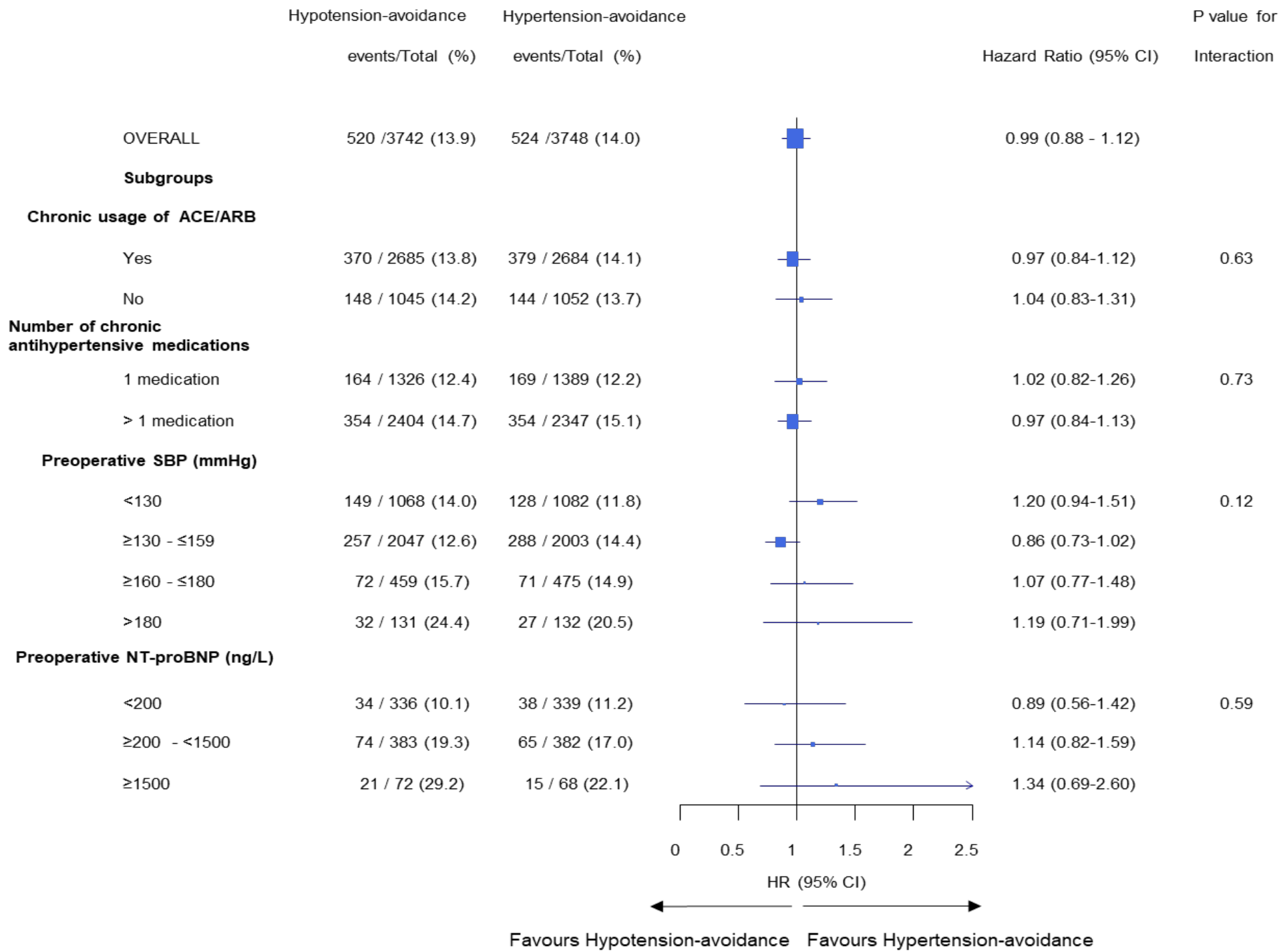
- Results not modified by status of randomization to tranexamic acid or placebo group (interaction P=0.54)

Secondary outcomes

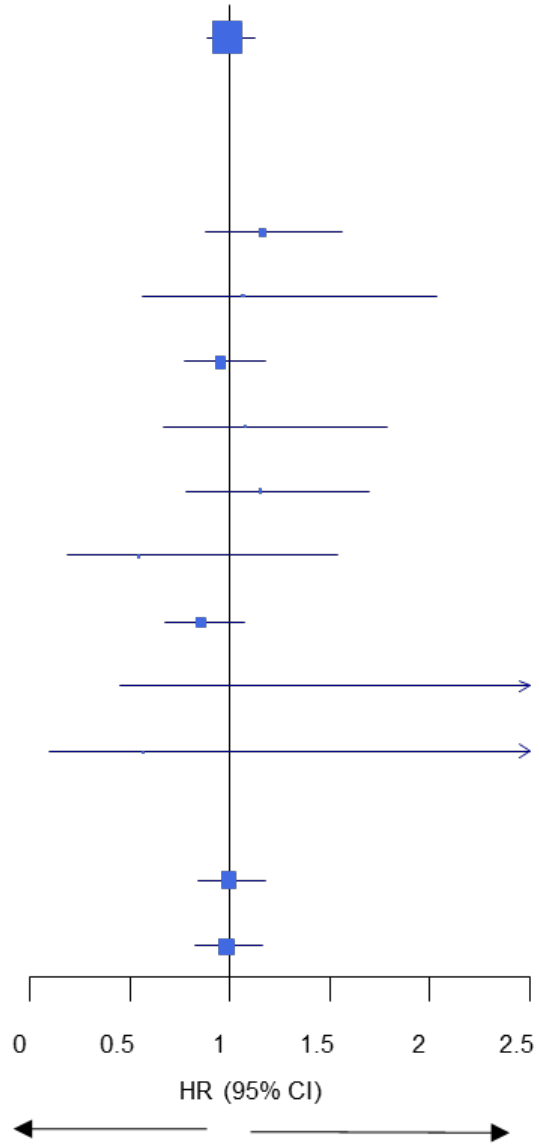
	Hypotension-avoidance N = 3742 n (%)	Hypertension-avoidance N = 3748 n (%)	Hazard ratio (95% CI)	P value
Myocardial injury after noncardiac surgery (MINS)	474 (12.7)	481 (12.8)	0.99 (0.87-1.12)	0.84
MINS not fulfilling universal definition of MI	424 (11.3)	439 (11.7)	0.97 (0.85-1.10)	0.61
Myocardial infarction	54 (1.4)	46 (1.2)	1.18 (0.80-1.75)	0.41
Stroke	17 (0.5)	17 (0.5)	1.00 (0.51-1.96)	>0.99
Vascular mortality	25 (0.7)	24 (0.6)	1.04 (0.60-1.83)	0.88
All-cause mortality	50 (1.3)	43 (1.1)	1.17 (0.78-1.75)	0.46

Tertiary outcomes

	Hypotension-avoidance N = 3742 n (%)	Hypertension-avoidance N = 3748 n (%)	Hazard ratio (95% CI)	P value
Non-fatal cardiac arrest	7 (0.2)	3 (<0.1)	2.34 (0.60-9.04)	0.22
Hemorrhagic stroke	0 (0.0)	1 (<0.1)	-	-
Non-hemorrhagic stroke	17 (0.5)	16 (0.4)	1.07 (0.54-2.11)	0.86
Acute congestive heart failure	21 (0.6)	18 (0.5)	1.17 (0.62-2.19)	0.63
New clinically important AF	62 (1.7)	44 (1.2)	1.42 (0.96-2.08)	0.08
Sepsis	47 (1.3)	57 (1.5)	0.88 (0.60-1.29)	0.51

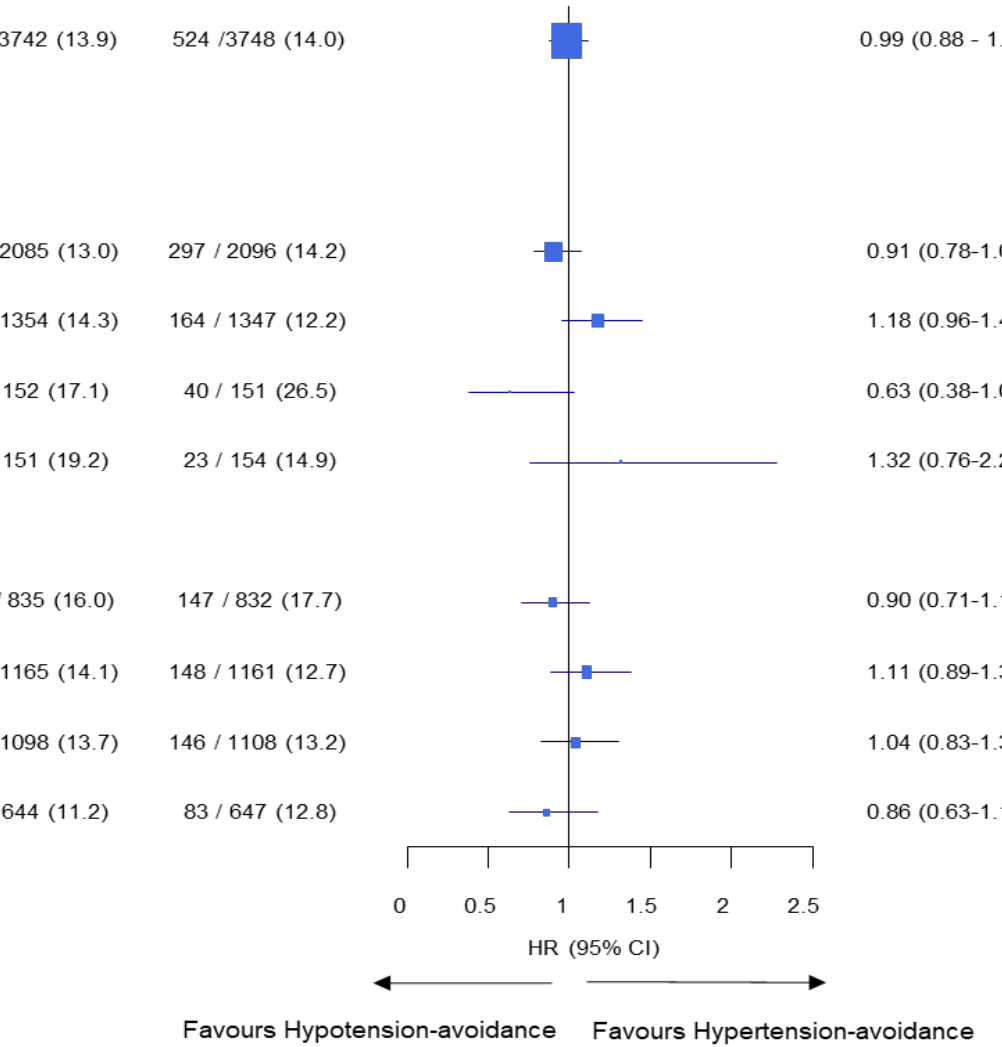

Hypotension-avoidance
events/Total (%)
Hypertension-avoidance
events/Total (%)
Hazard Ratio (95% CI)
P value for
Interaction
OVERALL
520 /3742 (13.9)
524 /3748 (14.0)
0.99 (0.88 - 1.12)
Subgroups
Chronic usage of ACE/ARB
Yes
370 / 2685 (13.8)
379 / 2684 (14.1)
0.97 (0.84-1.12)
0.63
No
148 / 1045 (14.2)
144 / 1052 (13.7)
1.04 (0.83-1.31)
Number of chronic antihypertensive medications
1 medication
164 / 1326 (12.4)
169 / 1389 (12.2)
1.02 (0.82-1.26)
0.73
> 1 medication
354 / 2404 (14.7)
354 / 2347 (15.1)
0.97 (0.84-1.13)
Preoperative SBP (mmHg)
<130
149 / 1068 (14.0)
128 / 1082 (11.8)
1.20 (0.94-1.51)
0.12
≥130 - ≤159
257 / 2047 (12.6)
288 / 2003 (14.4)
0.86 (0.73-1.02)
≥160 - ≤180
72 / 459 (15.7)
71 / 475 (14.9)
1.07 (0.77-1.48)
>180
32 / 131 (24.4)
27 / 132 (20.5)
1.19 (0.71-1.99)
Preoperative NT-proBNP (ng/L)
<200
34 / 336 (10.1)
38 / 339 (11.2)
0.89 (0.56-1.42)
0.59
≥200 - <1500
74 / 383 (19.3)
65 / 382 (17.0)
1.14 (0.82-1.59)
≥1500
21 / 72 (29.2)
15 / 68 (22.1)
1.34 (0.69-2.60)
0
0.5
1
1.5
2
2.5
HR (95% CI)
Favours Hypotension-avoidance
Favours Hypertension-avoidance

	Hypotension events/Total (%)	Hypertension events/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
OVERALL	520 /3742 (13.9)	524 /3748 (14.0)	0.99 (0.88 - 1.12)	
Subgroups				
Type of Surgery				
Vascular	95 / 533 (17.8)	85 / 542 (15.7)	1.16 (0.87-1.56)	0.68
Thoracic	21 / 97 (21.6)	17 / 86 (19.8)	1.07 (0.56-2.03)	
General	170 / 1341 (12.7)	181 / 1363 (13.3)	0.95 (0.77-1.17)	
Spinal	31 / 186 (16.7)	30 / 195 (15.4)	1.08 (0.66-1.79)	
Urology	54 / 493 (11.0)	47 / 491 (9.6)	1.15 (0.78-1.70)	
Gynecology	5 / 106 (4.7)	12 / 140 (8.6)	0.54 (0.19-1.54)	
Orthopedic	137 / 917 (14.9)	148 / 855 (17.3)	0.85 (0.67-1.07)	
Plastic	2 / 12 (16.7)	1 / 14 (7.1)	4.96 (0.45-55.0)	
Low risk	2 / 31 (6.5)	3 / 34 (8.8))	0.56 (0.09-3.43)	
Chronic usage of Beta Blocker				
Yes	267 / 1667 (16.0)	257 / 1601 (16.1)	0.99 (0.84-1.18)	0.88
No	251 / 2063 (12.2)	266 / 2135 (12.5)	0.98 (0.82-1.16)	



Effects on primary outcome by centre compliance

	Hypotension-avoidance events/Total (%)	Hypertension-avoidance events/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
OVERALL	520 /3742 (13.9)	524 /3748 (14.0)	0.99 (0.88 - 1.12)	
Subgroups				
Intraoperative Compliance(%)				
<60.0	272 / 2085 (13.0)	297 / 2096 (14.2)	0.91 (0.78-1.08)	0.05
≥60.0 and <70.0	193 / 1354 (14.3)	164 / 1347 (12.2)	1.18 (0.96-1.45)	
≥70.0 and <80.0	26 / 152 (17.1)	40 / 151 (26.5)	0.63 (0.38-1.03)	
≥80.0	29 / 151 (19.2)	23 / 154 (14.9)	1.32 (0.76-2.28)	
Pre-/Postoperative Compliance(%)				
<60.0	134 / 835 (16.0)	147 / 832 (17.7)	0.90 (0.71-1.13)	0.45
≥60.0 and <70.0	164 / 1165 (14.1)	148 / 1161 (12.7)	1.11 (0.89-1.39)	
≥70.0 and <80.0	150 / 1098 (13.7)	146 / 1108 (13.2)	1.04 (0.83-1.31)	
≥80.0	72 / 644 (11.2)	83 / 647 (12.8)	0.86 (0.63-1.18)	



Effects on hemodynamics

Post-randomization time	Hypotension-avoidance mean	Hypertension-avoidance mean	Mean difference (95% CI)
	Systolic blood pressure, mm Hg		
before anesthetic induction	147.5	146.5	1.0 (0.0, 2.0)
in PACU (2 hrs from surgery)	132.5	131.3	1.2 (0.1, 2.3)
upon arrival to surgical ward	132.1	130.4	1.7 (0.7, 2.7)
day 1 after surgery	129.0	127.4	1.6 (0.8, 2.4)
day 2 after surgery	131.8	130.7	1.1 (0.2, 2.0)
	Heart rate, bpm		
before anesthetic induction	75.4	74.8	0.6 (0.0, 1.2)
in PACU (2 hrs from surgery)	76.0	74.7	1.3 (0.5, 2.1)
upon arrival to surgical ward	76.6	75.2	1.4 (0.7, 2.1)
day 1 after surgery	77.0	75.8	1.2 (0.6, 1.8)
day 2 after surgery	78.7	77.3	1.4 (0.7, 2.1)

Effects on hemodynamics by centre compliance

- Effects of blood pressure strategies on hemodynamics consistent across centres with different compliance
  - Interaction P=0.72 for systolic blood pressure
  - Interaction P=0.15 for heart rate

Conclusions

- Perioperative hypotension-avoidance strategy did not differ from hypertension-avoidance strategy regarding effects on 30-day major vascular complications

Implications

- POISE-3 informs questions that commonly confront physicians taking care of patients undergoing surgery
  - during surgery: target MAPs ≥60 or ≥80 produced similar vascular outcomes
  - perioperatively: holding ACEI/ARBs and continuing other chronic antihypertensive meds based on blood pressure, versus continuing all antihypertensive meds, resulted in no substantial impact on hemodynamics and vascular outcomes
- Further research is needed to evaluate perioperative interventions that can modify hemodynamics to extent and in direction that will lead to favorable impact on clinical outcomes

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CHAP

Treatment For Mild Chronic Hypertension During Pregnancy

Open-Label, Multicenter, Randomized Trial

OBJECTIVE: To investigate a strategy of treating mild chronic hypertension during pregnancy with a blood pressure (BP) goal of less than 140/90 compared to a strategy of withholding treatment, and its effects on adverse maternal and perinatal outcomes.

2,408

INCLUSION CRITERIA: Pregnant women with new or known mild chronic hypertension (BP > 140/90), singleton fetuses at gestational age less than 23 weeks without high-risk comorbidities or complications warranting treatment at a lower BP or contraindication to first-line antihypertensive therapies.

ACTIVE TREATMENT TO BP LESS THAN 140/90 (N=1208)

VS.

STANDARD (CONTROL) TREATMENT OF WITHHOLDING THERAPY UNLESS BP OVER 160/105 DEVELOPED (N=1200)

PRIMARY ENDPOINT

COMPOSITE OF PREECLAMPSIA WITH SEVERE FEATURES, MEDICALLY INDICATED PRETERM BIRTH AT LESS THAN 35 WEEKS' GESTATION, PLACENTAL BRUPTION, OR FETAL OR NEONATAL DEATH

ACTIVE TREATMENT: 30.2% vs. **CONTROL GROUP: 37.0%**

SECONDARY ENDPOINT

SMALL-FOR-GESTATIONAL-AGE BIRTH WEIGHT BELOW THE 10TH PERCENTILE:

ACTIVE TREATMENT: 11.2% vs. **CONTROL GROUP: 10.4%**

CONCLUSION

Targeting a BP of less than 140/90 was associated with better pregnancy outcomes without increasing risk of small-for-gestational-age birth weight.

Tita AT, Szychowski JM, Boggess K, et al., on behalf of the Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for Mild Chronic Hypertension During Pregnancy. *N Engl J Med* 2022;Apr 2:[Epub ahead of print].

Developed and reviewed by Neil Keshvani, MD; Anthony A. Bavry, MD, MPH, FACC; and Deepak L. Bhatt, MD MPH, FACC

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PACMAN-AMI

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction

Double-Blind, Placebo-Controlled Randomized Trial

OBJECTIVE: To determine the effects of alirocumab administered within 24 hours on coronary atherosclerosis using serial intracoronary imaging in patients undergoing percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

300
PATIENTS

INCLUSION CRITERIA: Patients with successful PCI of culprit vessel for AMI and 2 non-infarct vessels with diameter stenosis 20-50% with LDL-C ≥ 125 mg/dl (off statin), or ≥ 70 mg/dl (on statin).

BIWEEKLY SUBCUTANEOUS ALIROCUMAB 150 MG (N=148)

VS.

PLACEBO (N=152)

PRIMARY ENDPOINT

CHANGE IN IVUS-DERIVED PERCENT ATHEROMA VOLUME FROM BASELINE TO WEEK 52:
ALIROCUMAB: -2.13% vs. **PLACEBO: -0.92%,**
DIFFERENCE: -1.21%, P<0.001

CONCLUSION

In patients with AMI undergoing PCI, biweekly subcutaneous alirocumab in addition to high-intensity statin therapy resulted in greater coronary plaque regression in non-infarct-related arteries after 52 weeks.

Räber L, Ueki Y, Otsuka T, et al., on behalf of the PACMAN-AMI Collaborators. Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial. *JAMA* 2022; Apr 3:[Epub ahead of print].

Developed and reviewed by Neil Keshvani, MD; Dharam J. Kumbhani, MD, SM, FACC; and Deepak L. Bhatt, MD, MPH, FACC

SCORED

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease – The SCORED Trial

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BWH

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Disclosures

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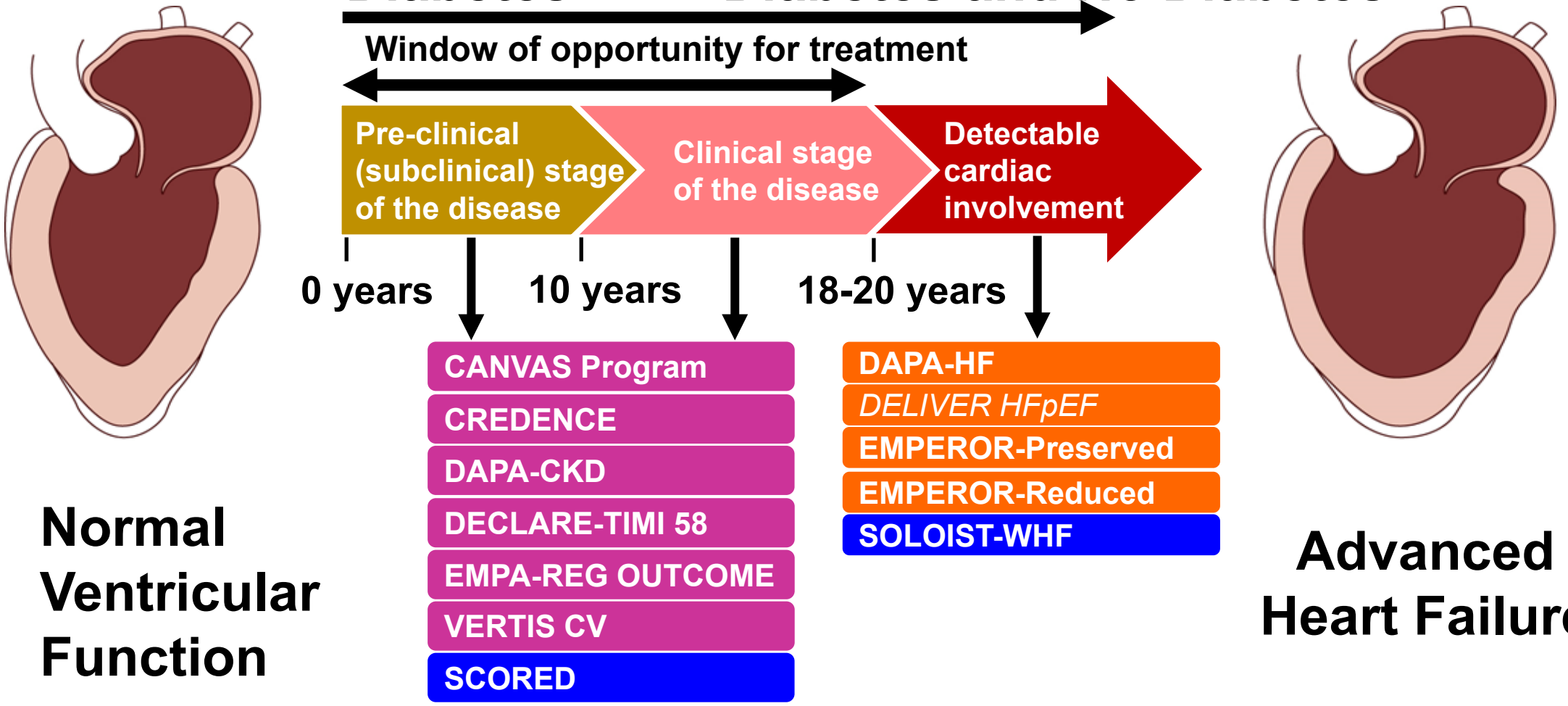
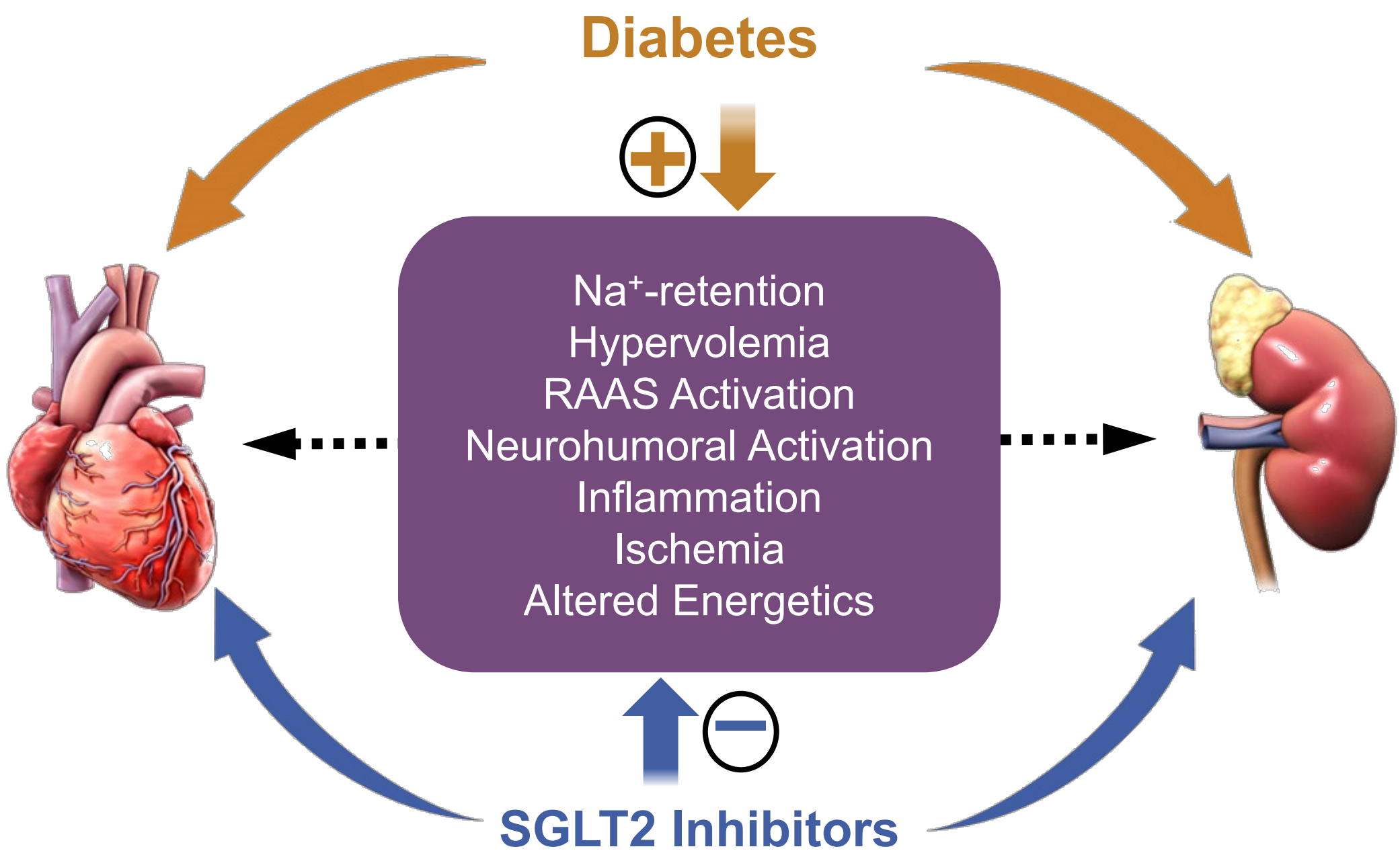
SCORED was initially sponsored by Sanofi and then by Lexicon.

This presentation includes off-label and investigational uses of drugs.

The Evolution of SGLT2i in Heart Failure Management

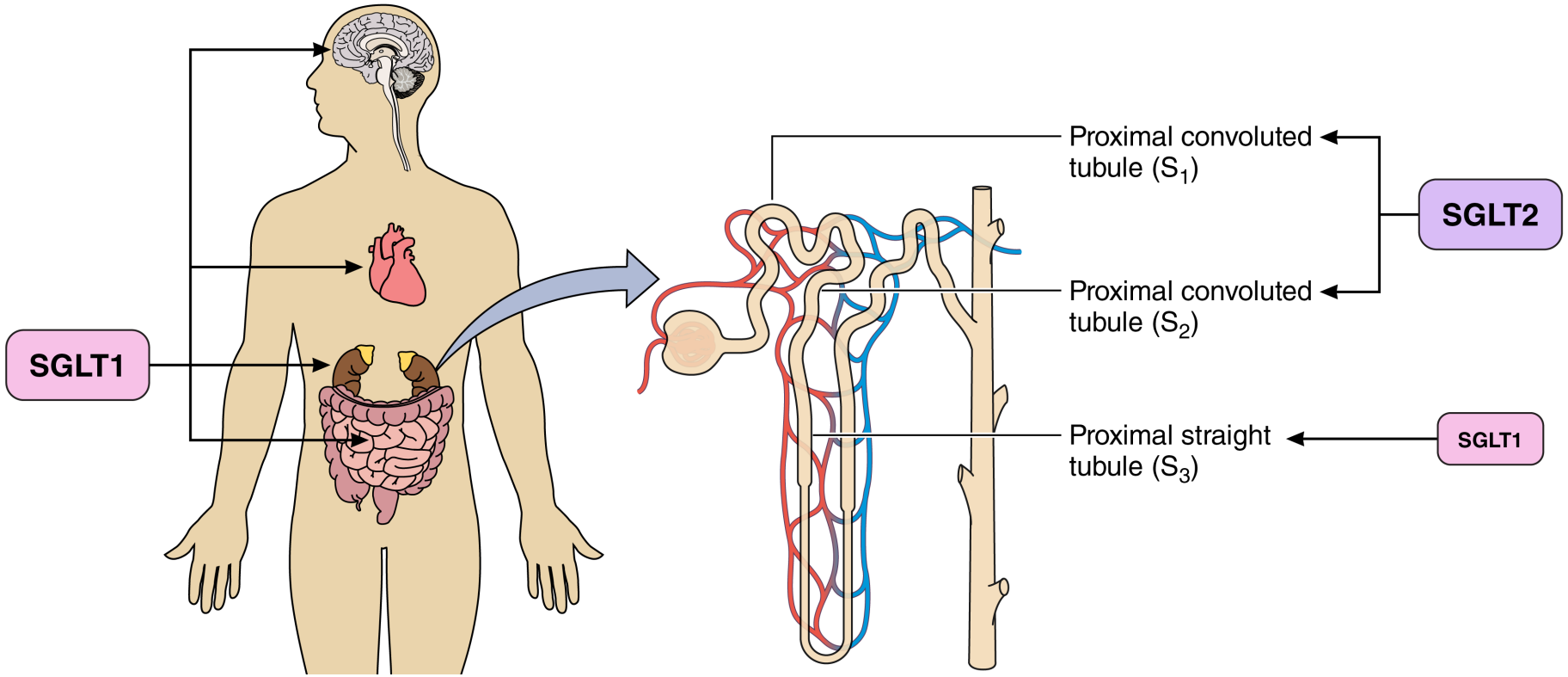


Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism*. 2019;30:847-849.



Connelly KA, Bhatt DL, Verma S. *Cell Metabolism*. 2018;28:813-815.

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor



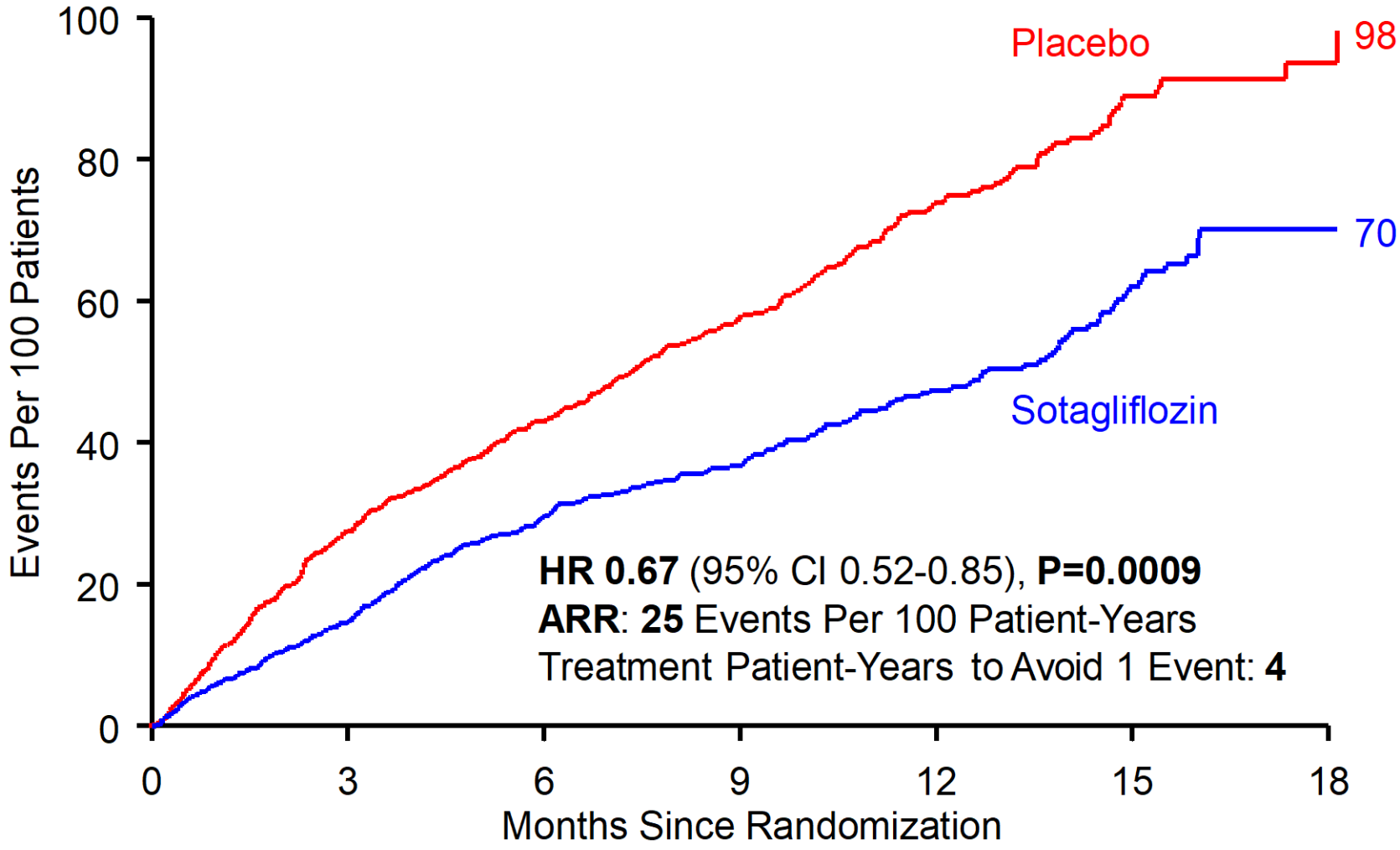
- **SGLT1** is the primary transporter for absorption of glucose and galactose in the GI tract
- Pharmacologic inhibition by sotagliflozin is independent of insulin and does not depend on kidney function
- Potential reduction in atherosclerotic risks

- **SGLT2** is expressed in the kidney, where it reabsorbs 90% of filtered glucose
- Pharmacologic inhibition by sotagliflozin is independent of insulin but requires kidney function

Pitt B, Bhatt DL. *Circulation*. 2021;144:4-6.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

SOLOIST

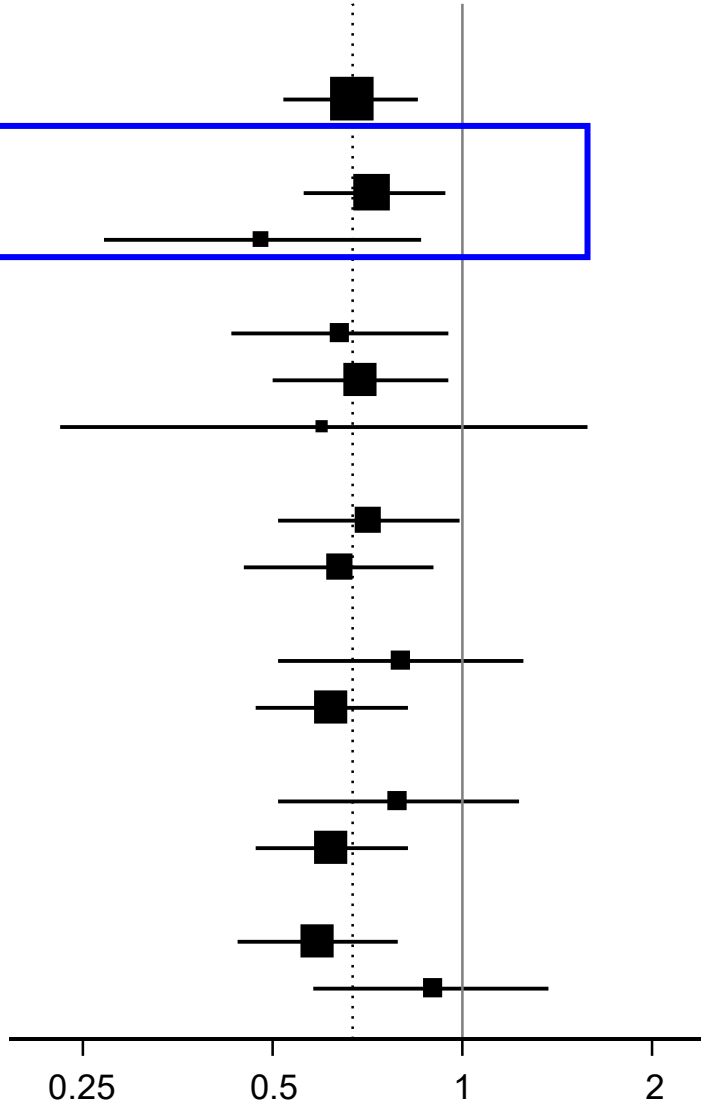


Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:117-28. Bhatt DL. AHA 2020, virtual.

Primary Efficacy Subgroups

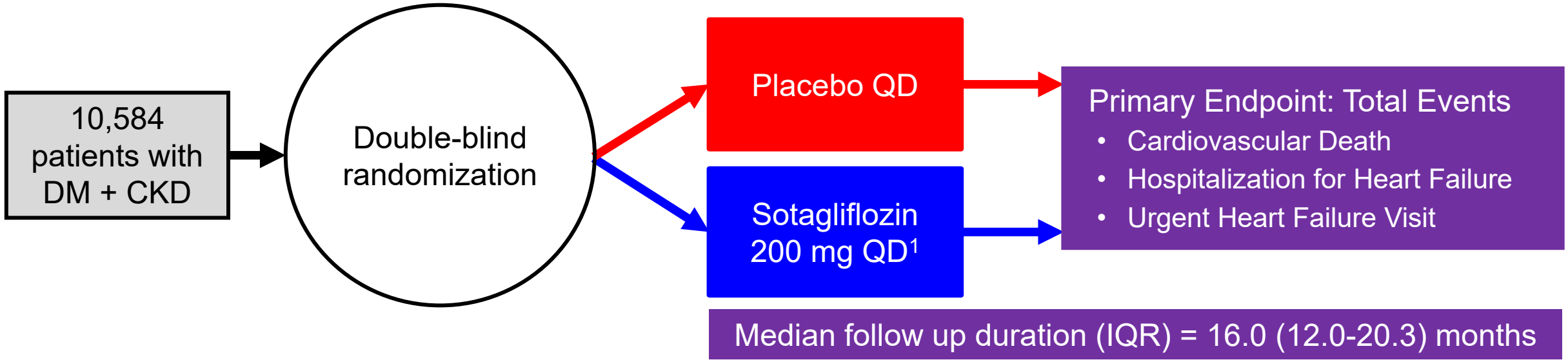
SOLOIST

Subgroup	Patients	Events Per 100 py: Sotagliflozin	Events Per 100 py: Placebo	HR (95% CI)
Overall	1222	51.0	76.3	0.67 (0.52, 0.85)
LVEF (%)				
< 50	966	56.9	79.9	0.72 (0.56, 0.94)
≥ 50	256	30.6	64.0	0.48 (0.27, 0.86)
Geographic Region				
Americas	346	68.3	103.0	0.64 (0.43, 0.95)
Europe	800	44.1	64.7	0.69 (0.50, 0.95)
Rest of World	76	48.4	78.3	0.60 (0.23, 1.58)
First Study Drug Dose				
Before Discharge	596	52.1	76.6	0.71 (0.51, 0.99)
After Discharge	626	50.0	76.1	0.64 (0.45, 0.90)
Sex				
Female	412	41.9	52.0	0.80 (0.51, 1.25)
Male	810	55.7	89.3	0.62 (0.47, 0.82)
Age (years)				
< 65	364	57.1	71.1	0.79 (0.51, 1.23)
≥ 65	858	48.0	78.5	0.62 (0.47, 0.82)
eGFR (ml/min/1.73m2)				
< 60	854	50.1	85.8	0.59 (0.44, 0.79)
≥ 60	368	53.1	58.1	0.90 (0.58, 1.37)



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021. Bhatt DL. AHA 2020, virtual.

SCORED Trial Design



Key inclusion criteria:

- Type 2 diabetes with HbA1c ≥ 7%
- eGFR 25-60 mL/min/1.73m^2
  - with no requirement for macro- or micro-albuminuria
- CV risk factors

Key exclusion criteria:

- Planned start of SGLT2 inhibitor

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2021. Bhatt DL. AHA 2020, virtual.

[1]Goal of dose increase to 400 mg QD

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

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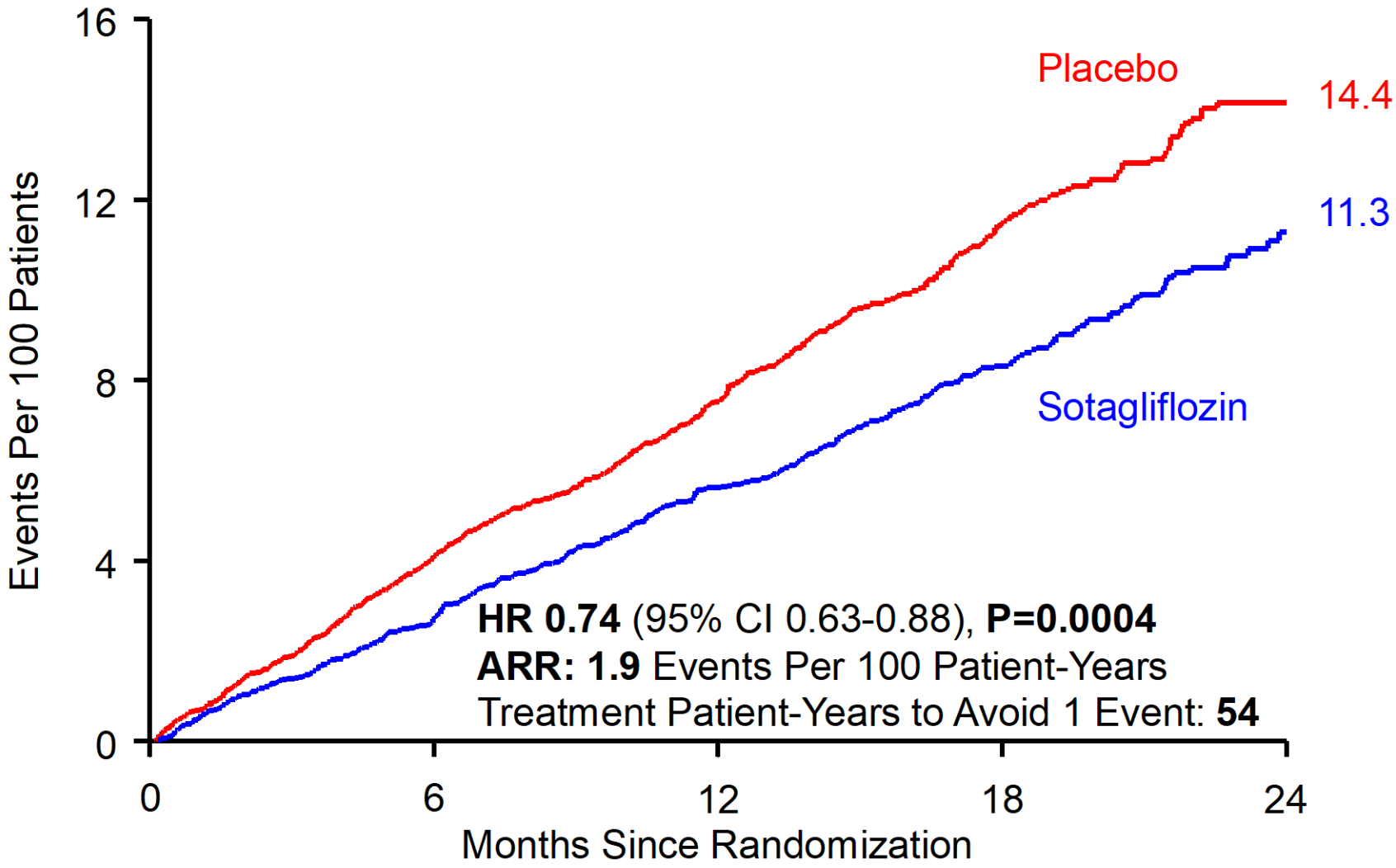

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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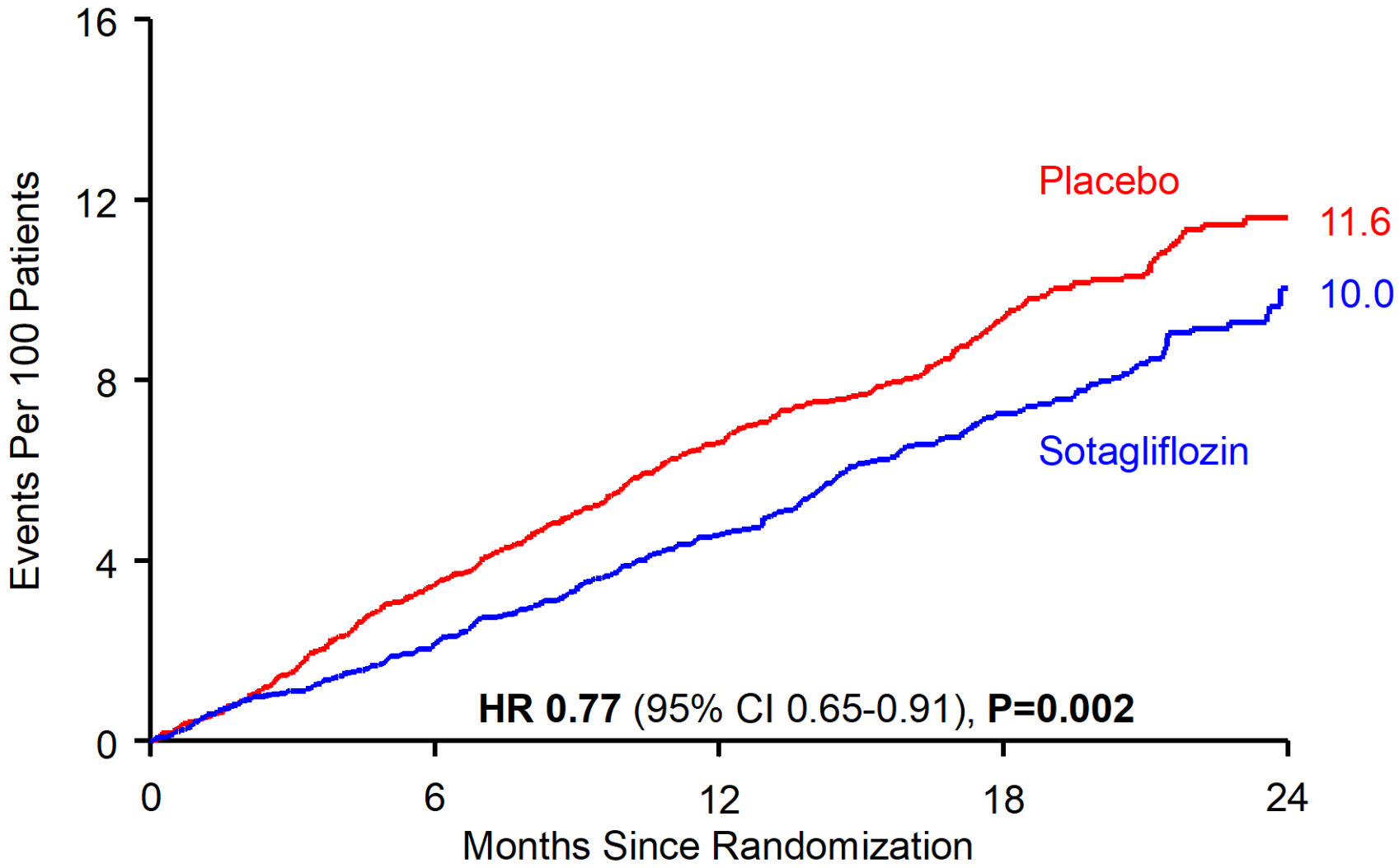

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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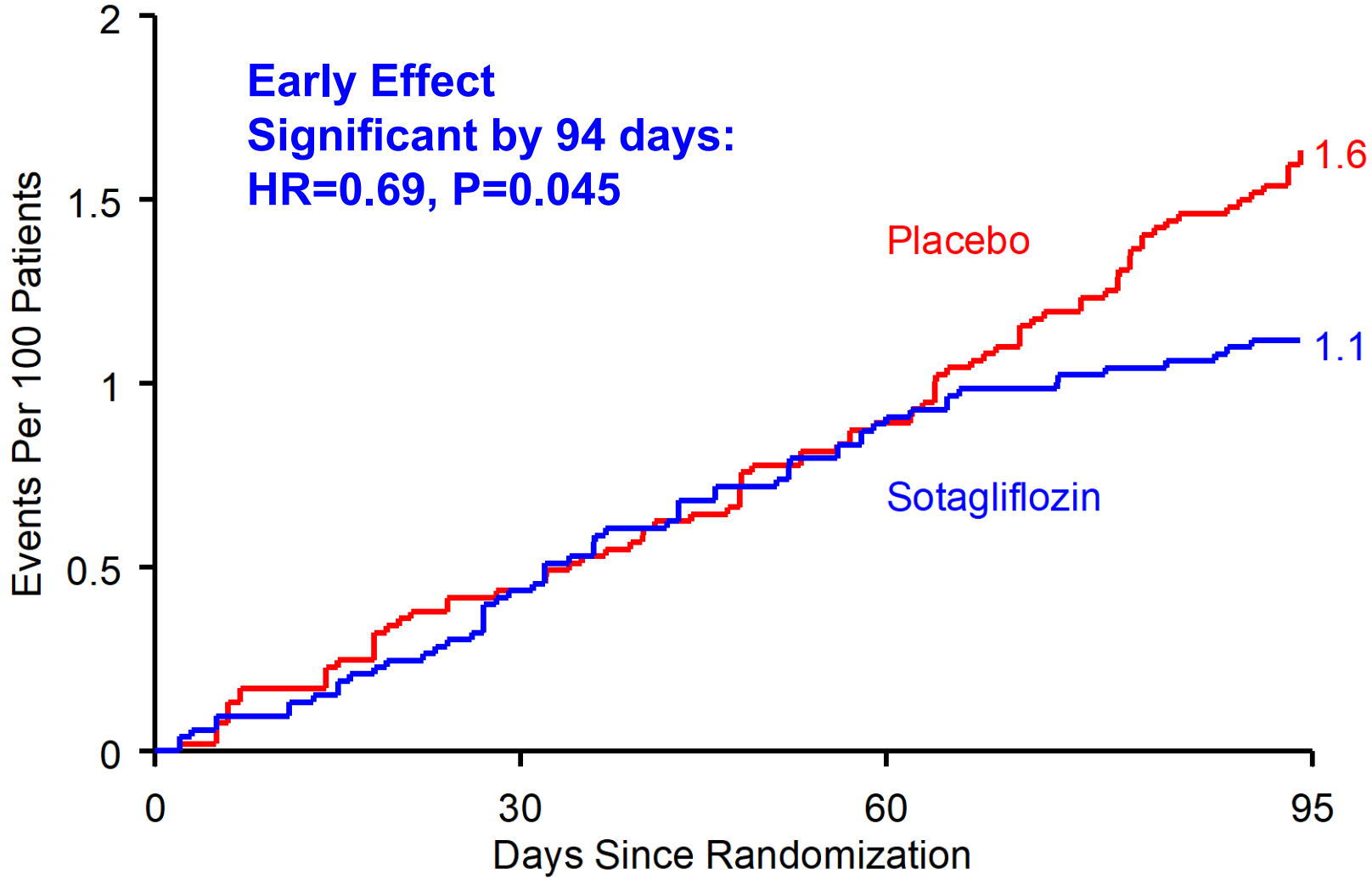

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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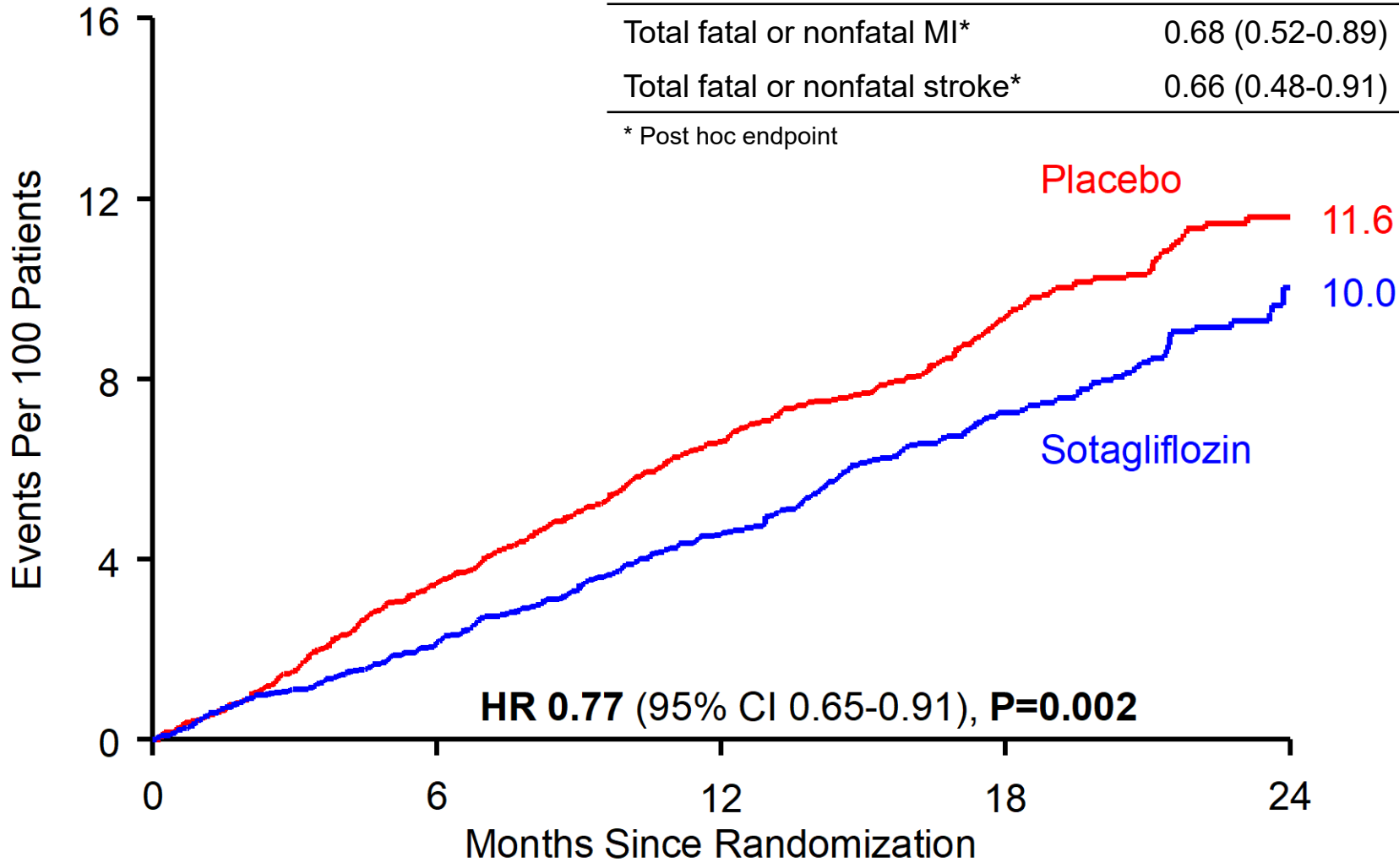
Endpoint	HR (95% CI)	P-value
Total fatal or nonfatal MI*	0.68 (0.52-0.89)	0.004
Total fatal or nonfatal stroke*	0.66 (0.48-0.91)	0.012

* Post hoc endpoint



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

History of Cardiovascular Disease (CVD) Subgroup Analyses

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Subgroups

1. History of cardiovascular disease at baseline (N=5144 patients)
2. No history of cardiovascular disease at baseline (N=5440 patients)

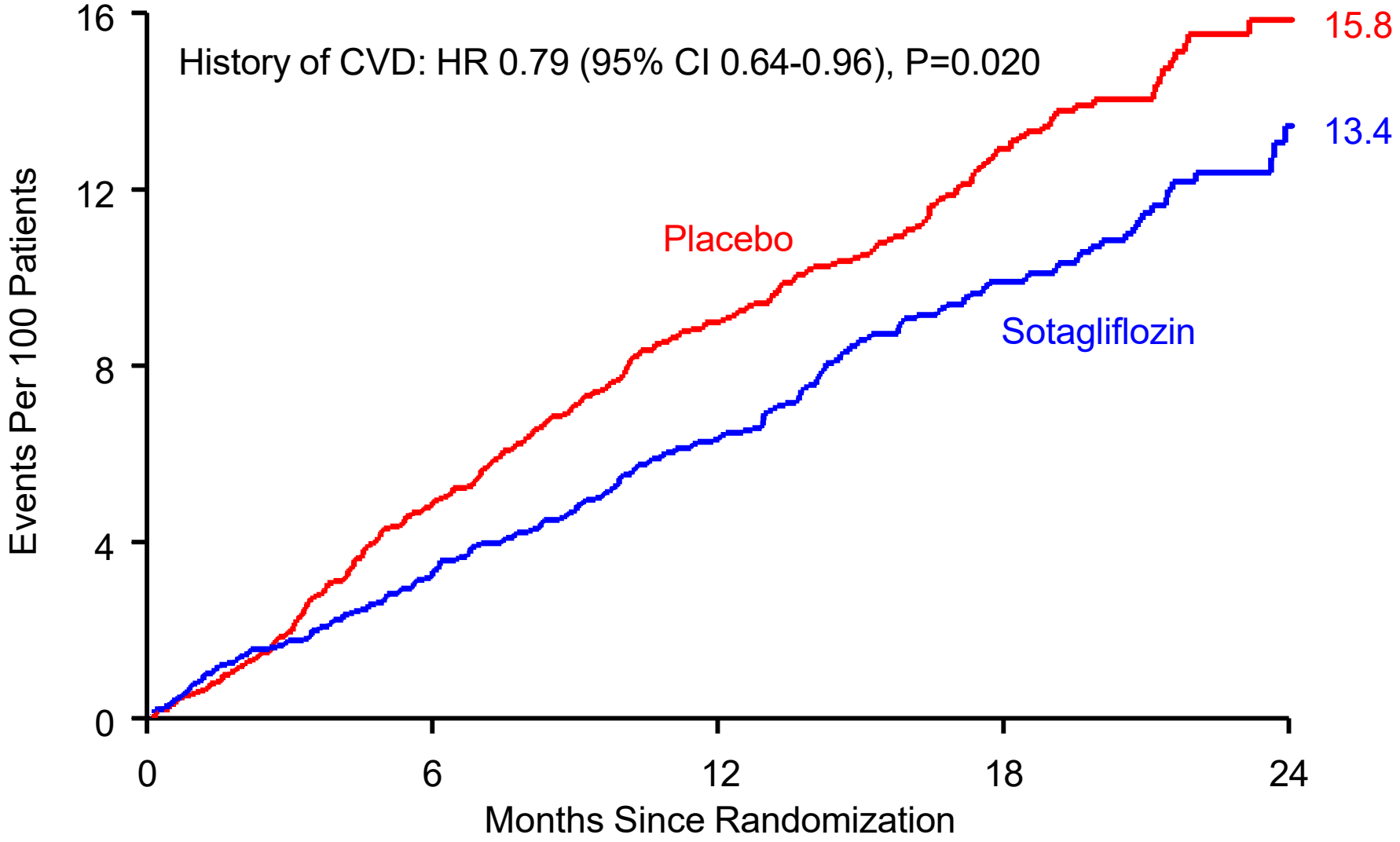
The prespecified definition of history of CVD included prior myocardial infarction, prior stroke, coronary revascularization, and peripheral vascular disease; (multiple *post hoc* sensitivity analyses yielded similar results)

Endpoints

1. Total MACE (first and recurrent events)
2. Total MI (fatal and non-fatal MI)
3. Total stroke (fatal and non-fatal stroke)

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. ACC 2022.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke by CVD Subgroup



Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke by CVD Subgroup

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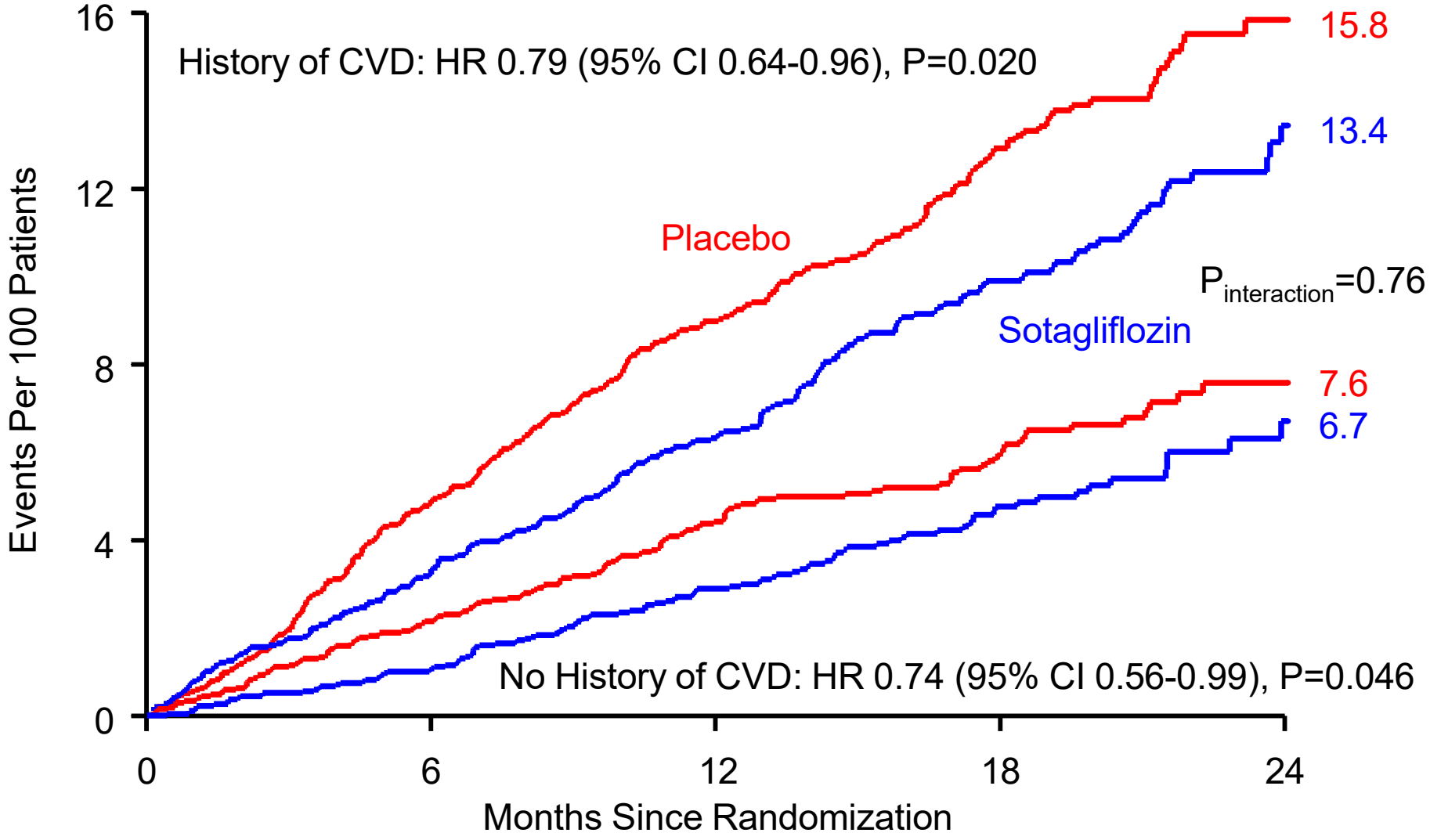

Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Total MI by CVD Subgroup

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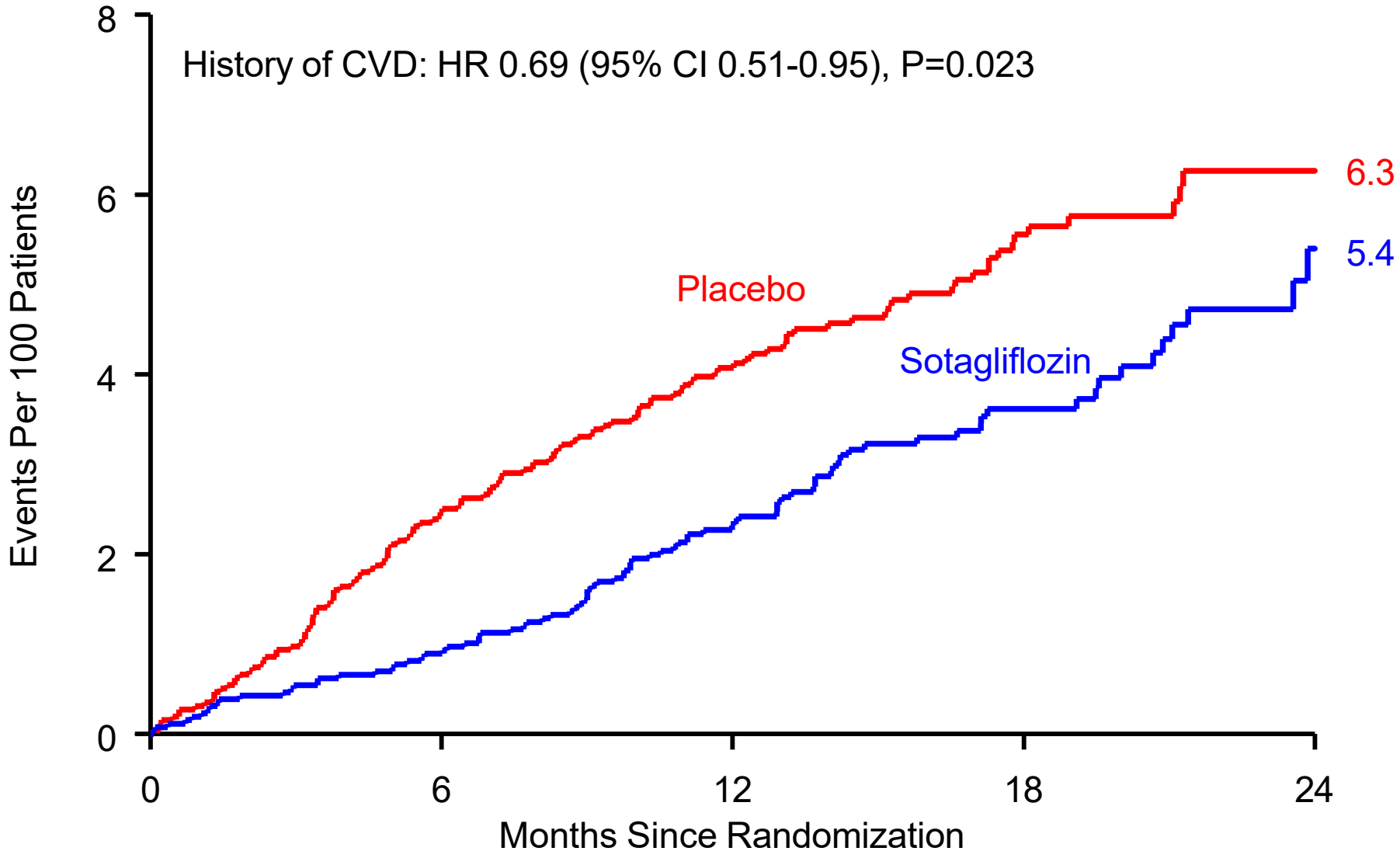

Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Total MI by CVD Subgroup

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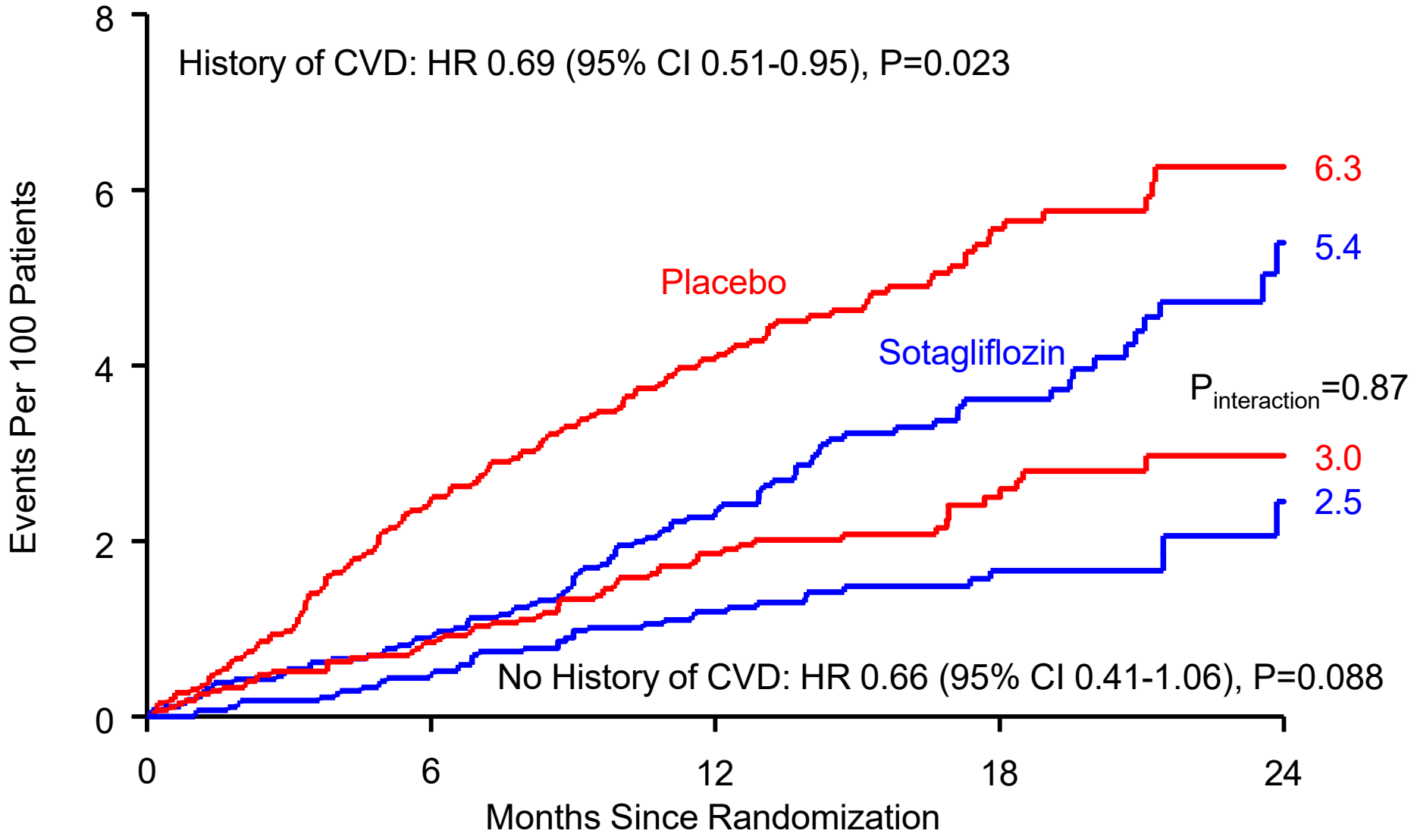

Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Total Stroke by CVD Subgroup

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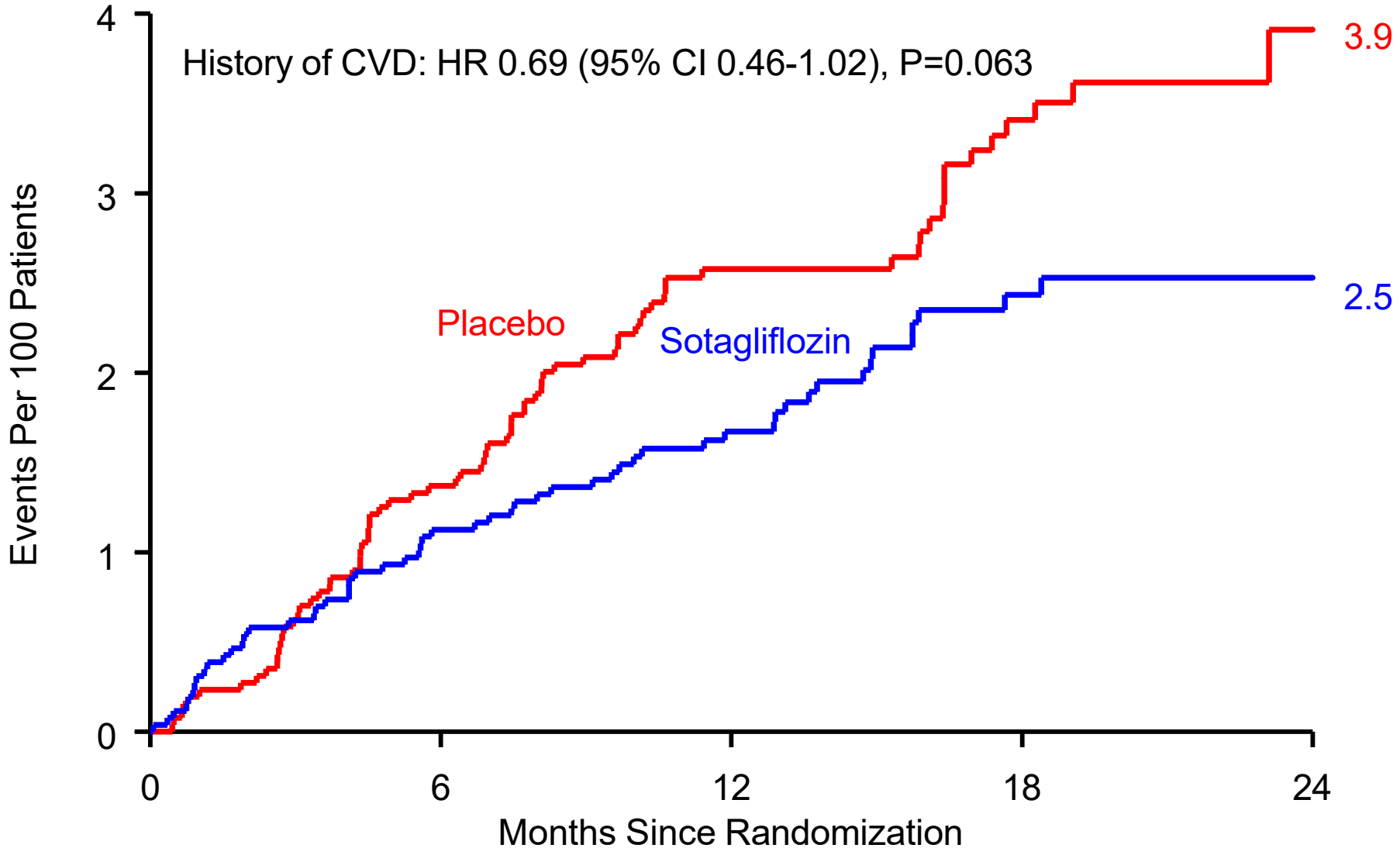

Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Total Stroke by CVD Subgroup

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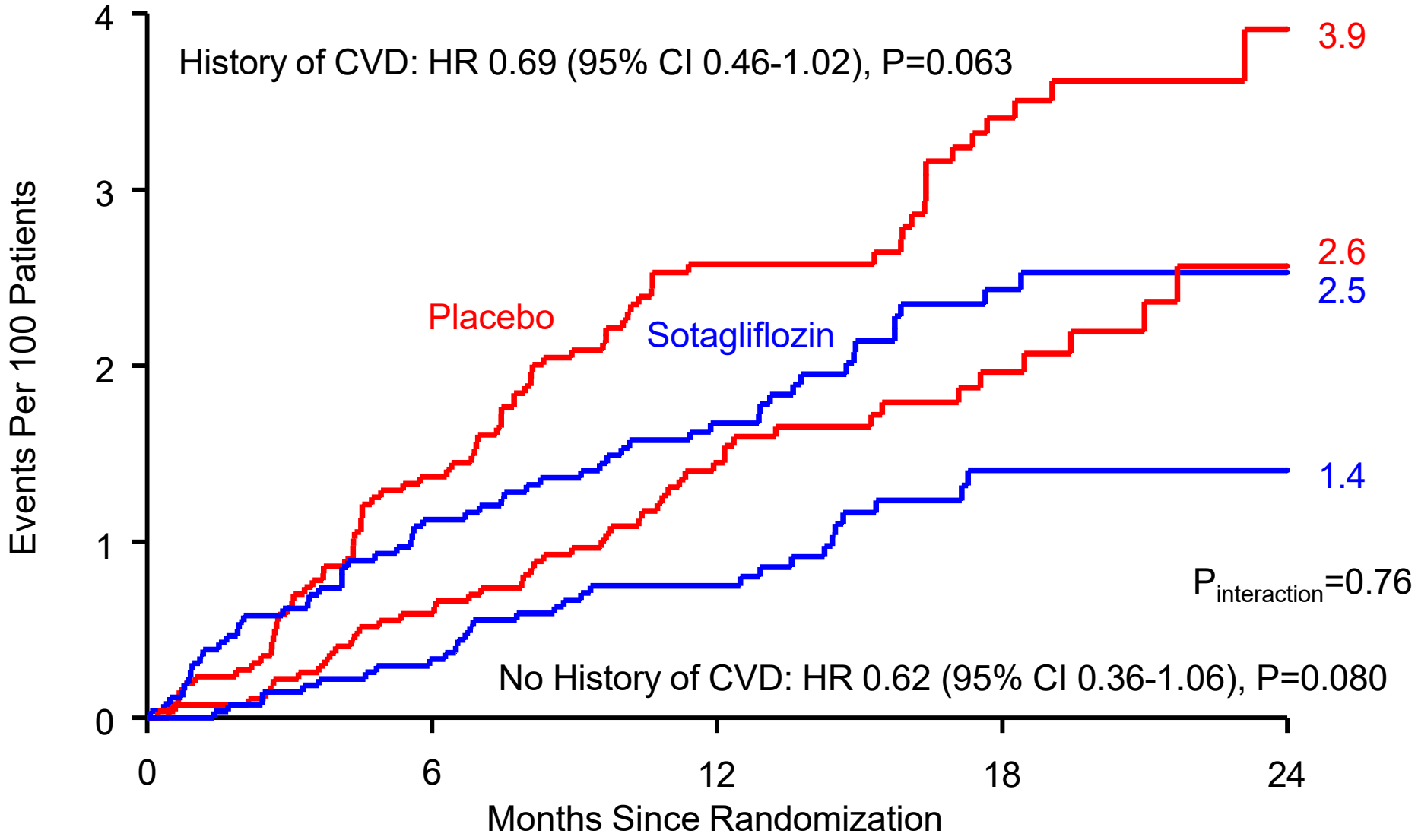

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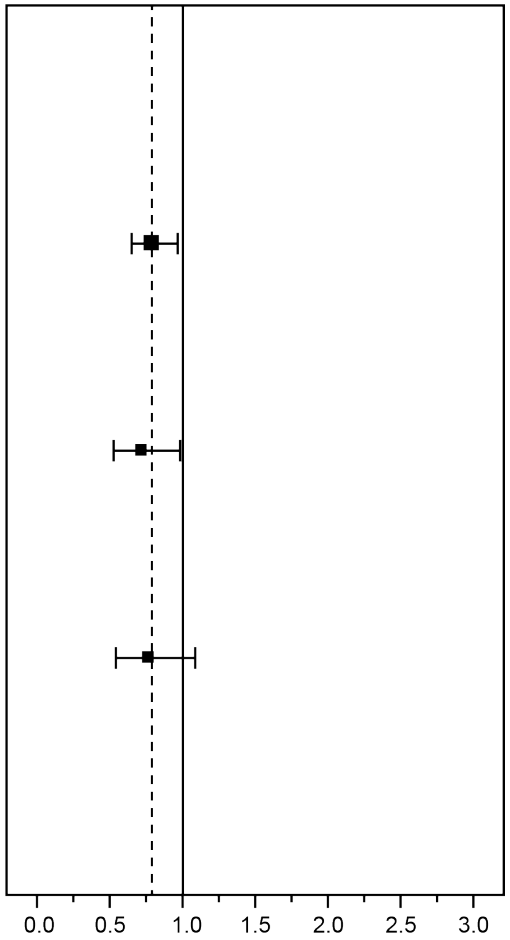
Consistent Benefit on MACE Across Vascular Beds

SCORED

Subgroup	N	Events Per 100 py: Sotagliflozin	Events Per 100 py: Placebo	HR (95% CI)	p-value
Coronary Artery Disease	4943	6.13	7.77	0.79 (0.65, 0.97)	0.022
Cerebrovascular Disease	1777	7.03	9.54	0.72 (0.53, 0.99)	0.042
Peripheral Artery Disease	1393	6.76	9.50	0.77 (0.54, 1.09)	0.140

$P_{interaction}$=NS for all comparisons



Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Adverse Events of Special Interest

SCORED

Composite Term	Sotagliflozin N=5291 n (%)	Placebo N=5286 n (%)	P-value
Urinary tract infections	610 (11.5)	585 (11.1)	0.45
Diarrhea	448 (8.5)	315 (6.0)	<0.0001*
Volume depletion	278 (5.3)	213 (4.0)	0.003*
Bone fractures	111 (2.1)	117 (2.2)	0.68
Genital mycotic infections	125 (2.4)	45 (0.9)	<0.0001*
Severe hypoglycemia	53 (1.0)	55 (1.0)	0.84
Malignancies	47 (0.9)	42 (0.8)	0.60
Venous thrombotic events	31 (0.6)	37 (0.7)	0.46
Adverse event leading to amputation	32 (0.6)	33 (0.6)	0.89
Diabetic ketoacidosis	30 (0.6)	14 (0.3)	0.022*
Pancreatitis	12 (0.2)	20 (0.4)	0.16

*Proportions considered serious were similar between groups, and adverse events generally did not lead to treatment discontinuation

Bhatt DL, et al. *N Engl J Med.* 2021;384:129-39.

Meta-analysis of MACE Across Sotagliflozin Trials (N>20,000)

SCORED

Study Cohort	Sotagliflozin	Placebo	HR (95% CI)
SCORED (N = 10,584) Total events (rate/100 PY)*	N = 5,292 343 (4.8)	N = 5,292 442 (6.3)	0.77 (0.65, 0.91)
SOLOIST (N = 1,222) Total events (rate/100 PY)*	N = 608 83 (17.4)	N = 614 80 (17.2)	0.99 (0.72, 1.37)
Core Phase 3 T2DM (N = 5,100) Total events (rate/100 PY)**	N = 2,904 55 (1.6)	N = 2,196 50 (2.1)	0.63 (0.42, 0.94)
Core Phase 3 T1DM, Phase 2 T2DM (N = 3,386) Total events (rate/100 PY)**	N = 1,998 9 (0.69)	N = 1,388 8 (0.87)	0.68 (0.25, 1.82)
Meta-analysis results (N=20,292)			**0.79 (0.68, 0.90)**

*Investigator-reported events; **Adjudicated events

Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Limitations

SCORED

Trial was stopped early

- Shortened duration limited the statistical power to see significant reductions in CV death
- Limited the magnitude of absolute risk reductions in MACE

Investigator-reported events were used instead of adjudication

- Double-blind trial, with no reason to expect bias
- Results were generally concordant

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

Conclusions

SCORED

In patients with diabetes and chronic kidney disease, **sotagliflozin** significantly reduced the composite of total CV deaths, hospitalizations for HF, and urgent HF visits by **26%**

- With a very early benefit that was **significant by ~3 months**

Total CV deaths, MIs, and strokes were reduced by **23%**, potentially due to the SGLT1 effect of **sotagliflozin** **on MI and also stroke; this effect was significant by ~ 3 months**

MACE benefits were consistent across subgroups, including:

- **Prior coronary, cerebral, or peripheral artery disease**
- **And even without established cardiovascular disease**

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. ACC 2022.

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

ACC – Washington DC Monday April 4, 2022
Featured Clinical Research – Late Breaking Clinical Trials

Residual Inflammatory Risk and Residual Cholesterol Risk Among Statin Treated Atherosclerosis Patients With and Without Chronic Kidney Disease:

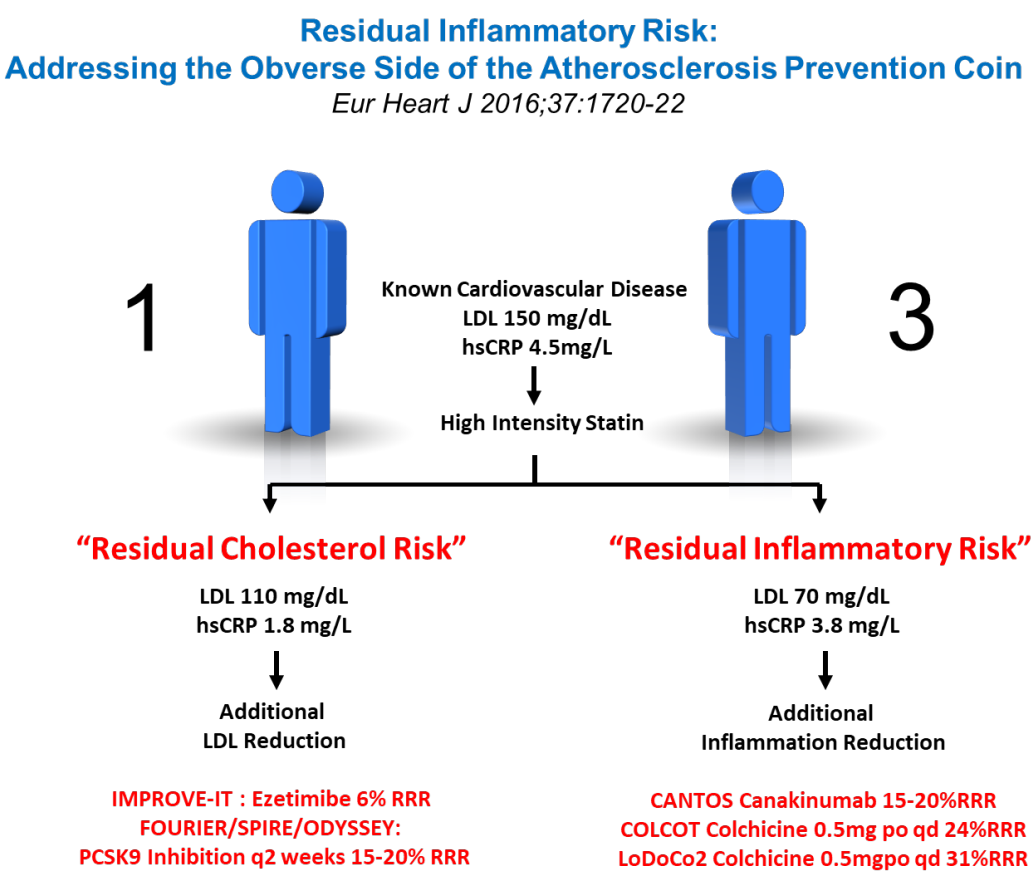
A Secondary Analysis of CANTOS

Paul M Ridker, Katherine Tuttle, Vlado Perkovic, Peter Libby,
G Kees Hovingh, Jean G MacFadyen on behalf of the
CANTOS CKD Investigators

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S
Department of Medicine

HARVARD
MEDICAL SCHOOL
Global and Continuing
Education

Residual Inflammatory Risk and Residual Cholesterol Risk in the Contemporary Care of Atherosclerosis



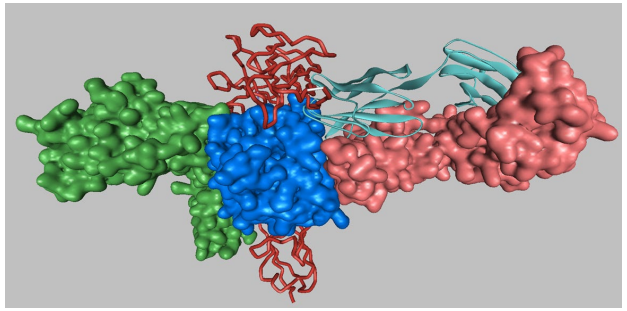
Ridker PM. Eur Heart J 2016;37:1720-22

Hyperlipidemia and inflammation jointly contribute to atherosclerotic disease and both have proven to be effective targets for pharmacologic and non-pharmacologic interventions.

Yet, the relative contributions of these processes may differ in important ways in various patient groups, such as those with impaired kidney function, a group with very high risk for atherosclerotic events and substantial unmet clinical need.

We therefore sought to assess the relative impact of residual inflammatory risk and residual cholesterol risk in a contemporary large-scale cohort of atherosclerosis patients already treated with guideline lipid lowering therapy.

Canakinumab, a Human Monoclonal Antibody Neutralizing IL-1β



CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Stable CAD (post MI)
Residual Inflammatory Risk
(hsCRP ≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

- Randomized Canakinumab 50 mg SC q 3 months
- Randomized Canakinumab 150 mg SC q 3 months
- Randomized Canakinumab 300 mg SC q 3 months
- Randomized Placebo SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

Additional Adjudicated Endpoints: Cancer, Infection

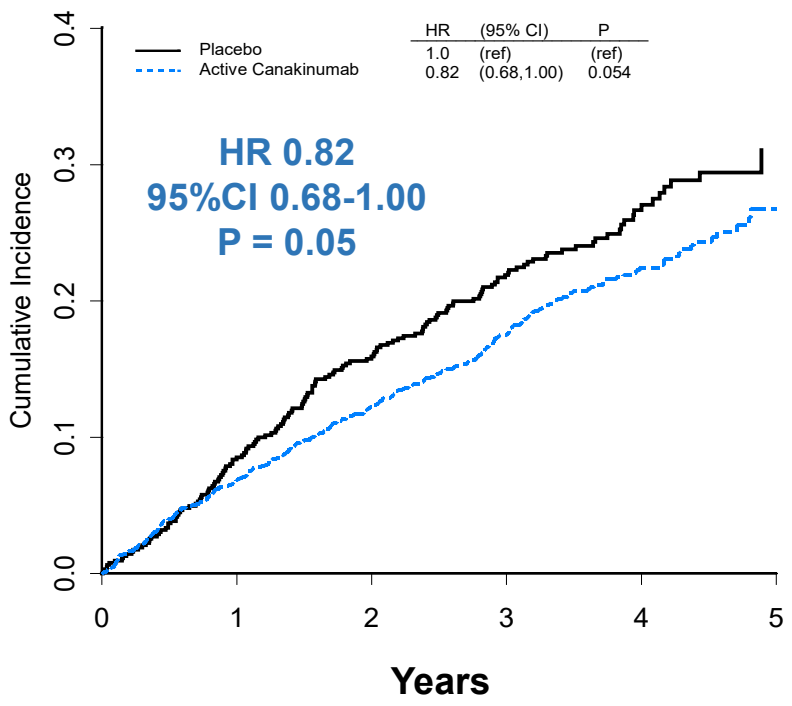
		Canakinumab SC q 3 months		
Characteristic	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)
Age (years)	61.1	61.1	61.2	61.1
Female (%)	25.9	24.9	25.2	26.8
Current smoker (%)	22.9	24.5	23.4	23.7
Diabetes (%)	39.9	39.4	41.8	39.2
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6
Prior Revascularization (%)	79.6	80.9	82.2	80.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0
Triglycerides (mg/dL)	139	139	139	138
hsCRP (mg/L)	4.1	4.1	4.2	4.1

MACE+
(150, 300 mg doses vs placebo)
HR 0.83, 95%CI 0.74-0.92, P=0.0006

Ridker et al N Engl J Med. 2017;377:1119-31

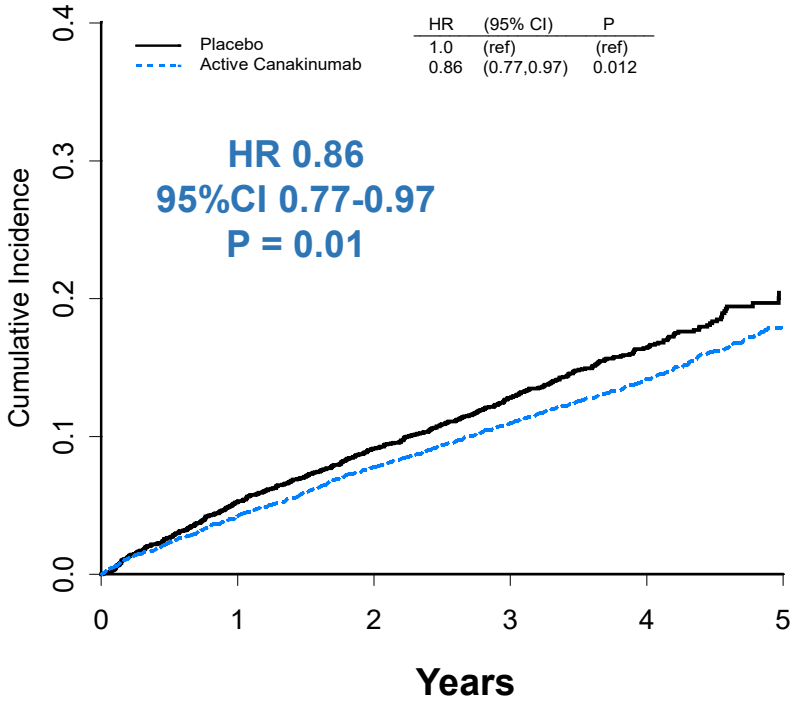
CANTOS – CKD Substudy : Primary Cardiovascular Results Stratified by Baseline eGFR

eGFR < 60 mL/min/1.73m2



Moderate CKD
(N = 1,192)

eGFR ≥ 60 mL/min/1.73m2



Normal Renal Function
(N = 7,949)

Ridker et al JACC 2018;71:2405-14

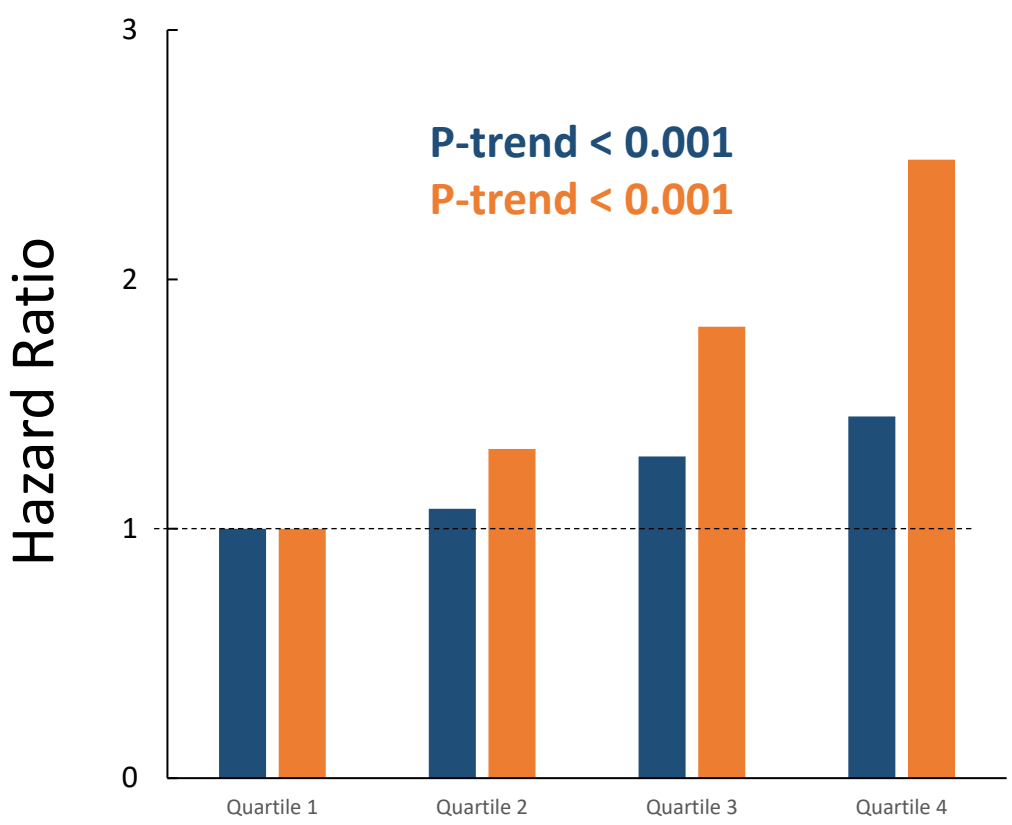
Residual Inflammatory Risk and Residual Cholesterol Risk Among Statin Treated Atherosclerosis Patients With and Without Chronic Kidney Disease

Methods: Among 9,151 stable statin treated post-myocardial infarction patients being randomized into CANTOS, we compared the relative contributions of residual cholesterol risk and residual inflammatory risk as determinants of recurrent major adverse cardiovascular events (MACE), CV death, and total mortality, stratified by baseline estimated glomerular filtration rate (eGFR) above or below 60 mL/min/1.73m^2 using the race agnostic CKD-EPI 2021 formula.

Biomarkers: Analyses of inflammation focused on high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) while lipid analyses focused on low-density lipoprotein cholesterol (LDLC) and non-high-density lipoprotein cholesterol (non-HDLC). All measures performed in a core laboratory.

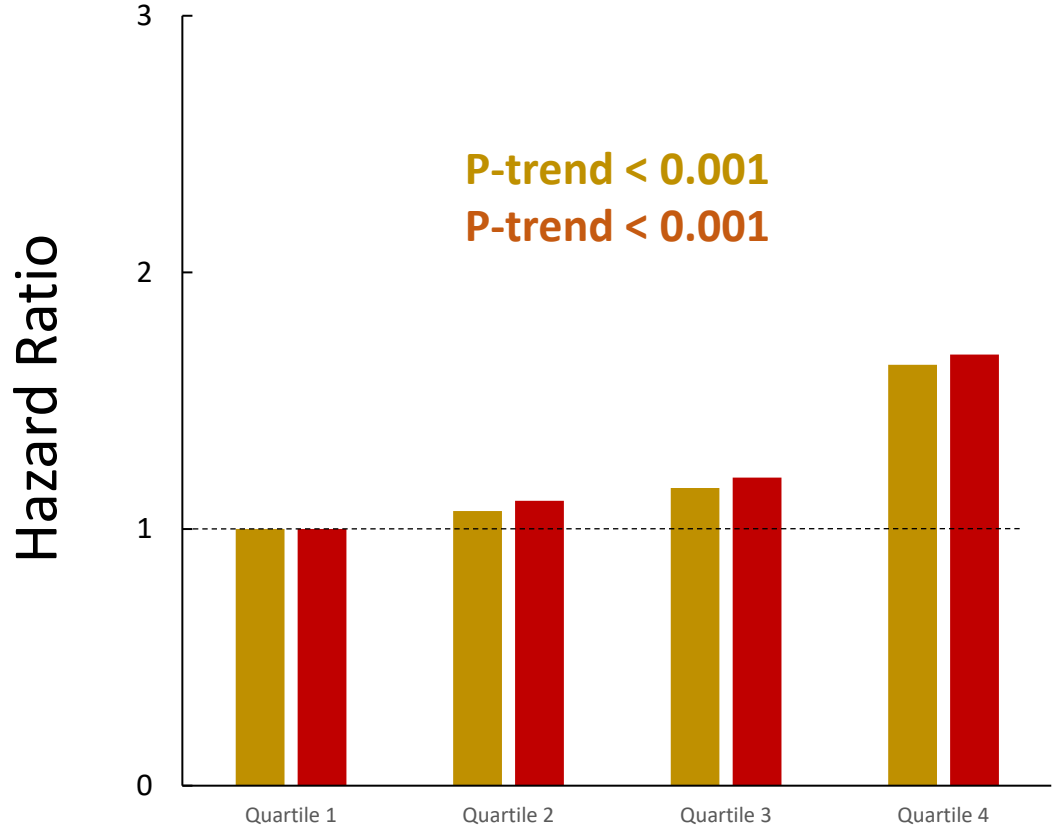
Outcomes and Analysis: Participants were followed for a period of up to 5 years. Primary analyses focused on major adverse cardiovascular events, CV mortality and all-cause mortality both in univariate and multivariate analyses, as well as addressing for joint effects across stratum of eGFR. All analyses additionally controlled for randomized treatment assignment.

Results I: Predictive utility of hsCRP, IL-6, LDLC, and non-HDLC for recurrent major adverse cardiovascular events (MACE) among participants with preserved kidney function (eGFR >60 ml/min/1.73m^2) (N = 7,949)



hsCRP

IL-6



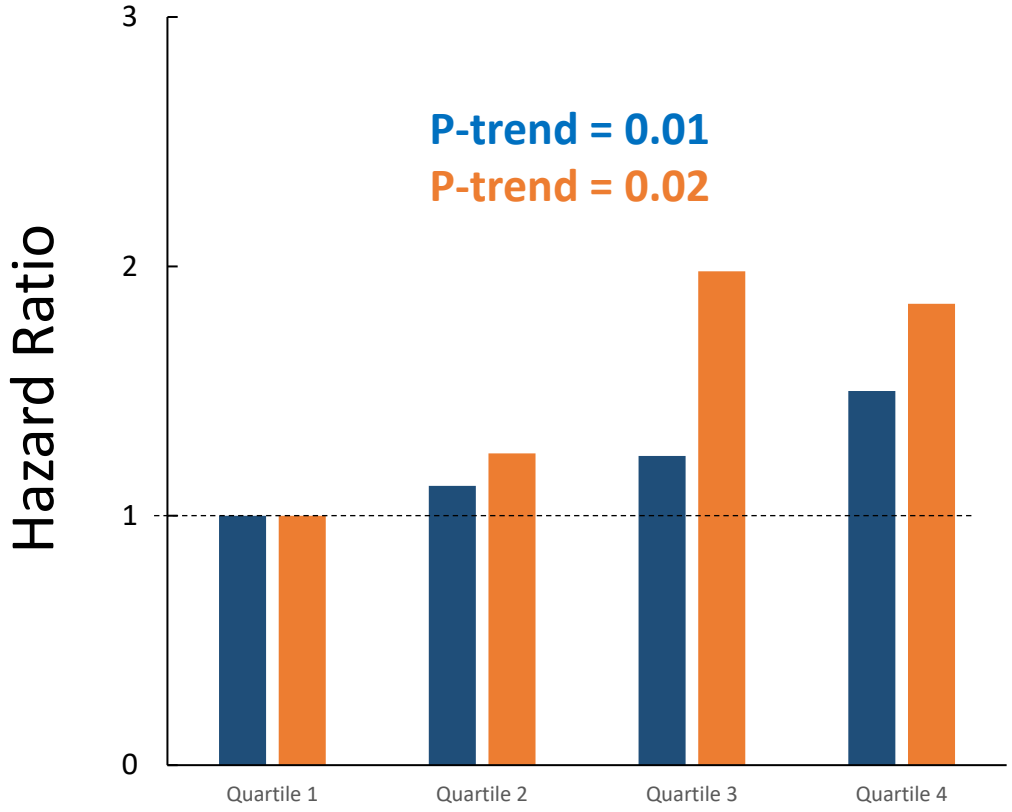
LDLC

Non-HDLC

MACE

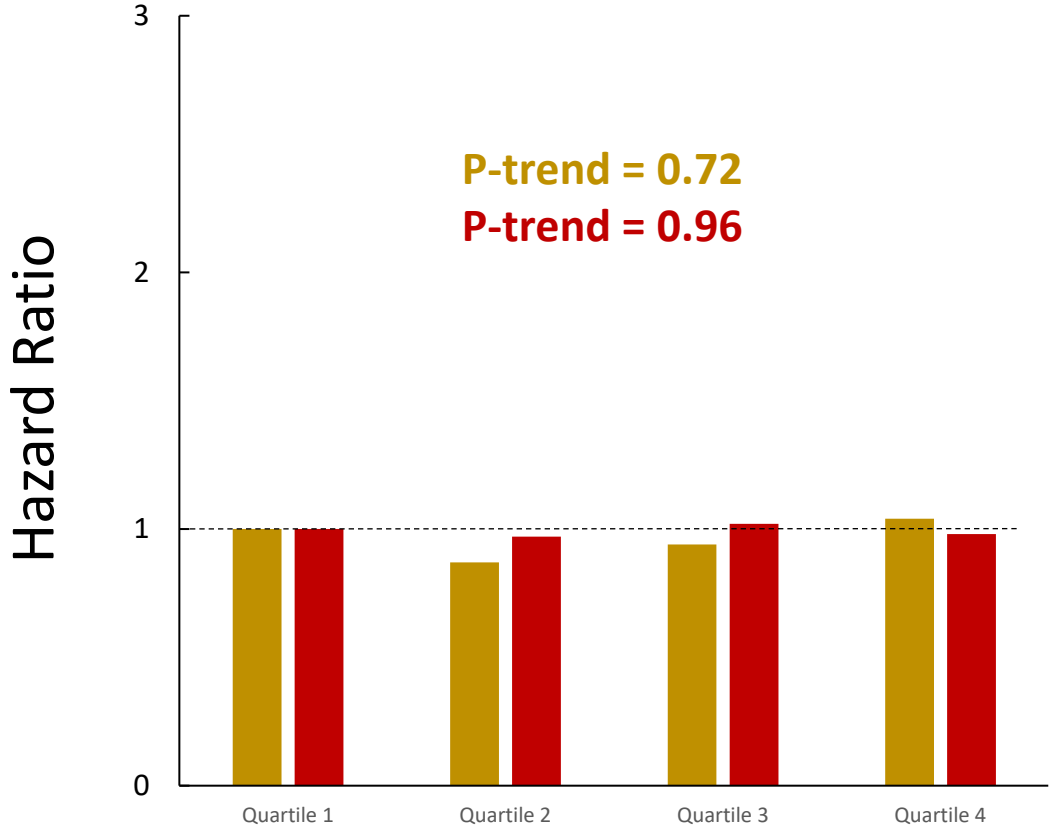
Preserved Kidney Function

Results II: Predictive utility of hsCRP, IL-6, LDLC, and non-HDLC for recurrent major adverse cardiovascular events (MACE) among participants with impaired kidney function (eGFR <60 ml/min/1.73m²) (N = 1,192)



hsCRP

IL-6



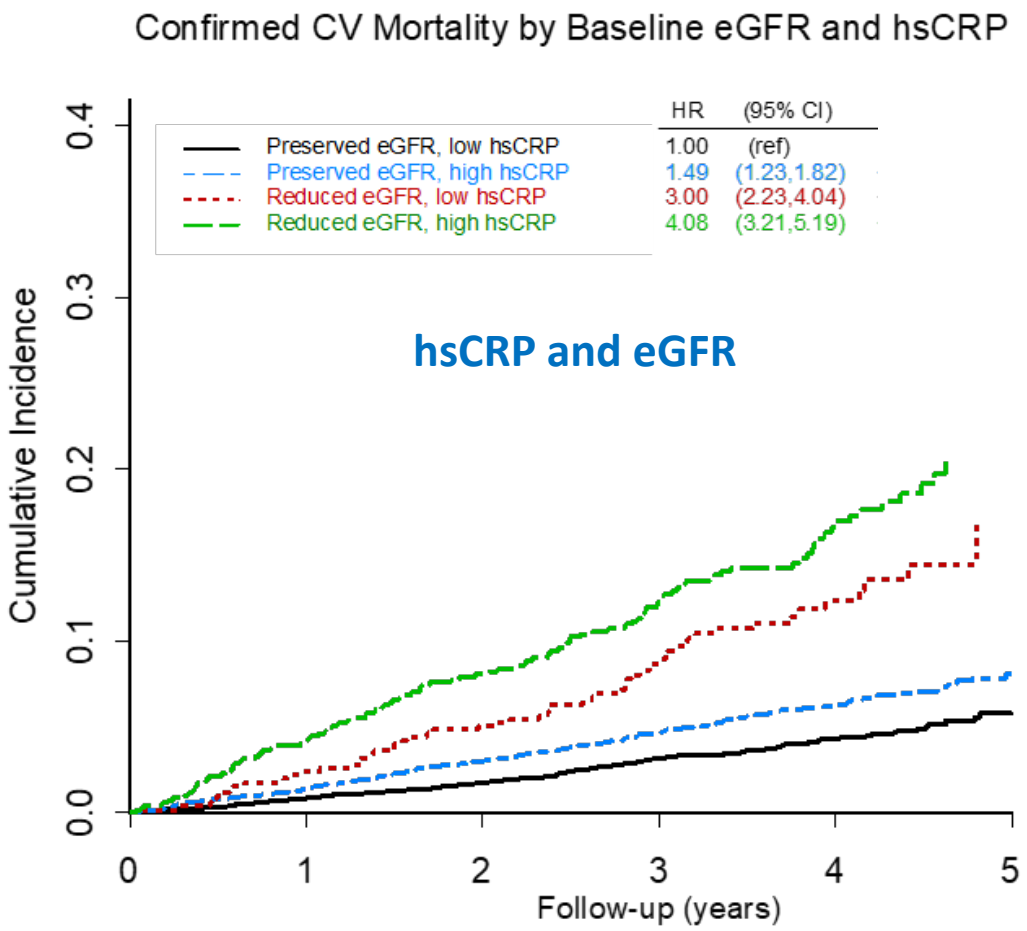
LDLC

Non-HDLC

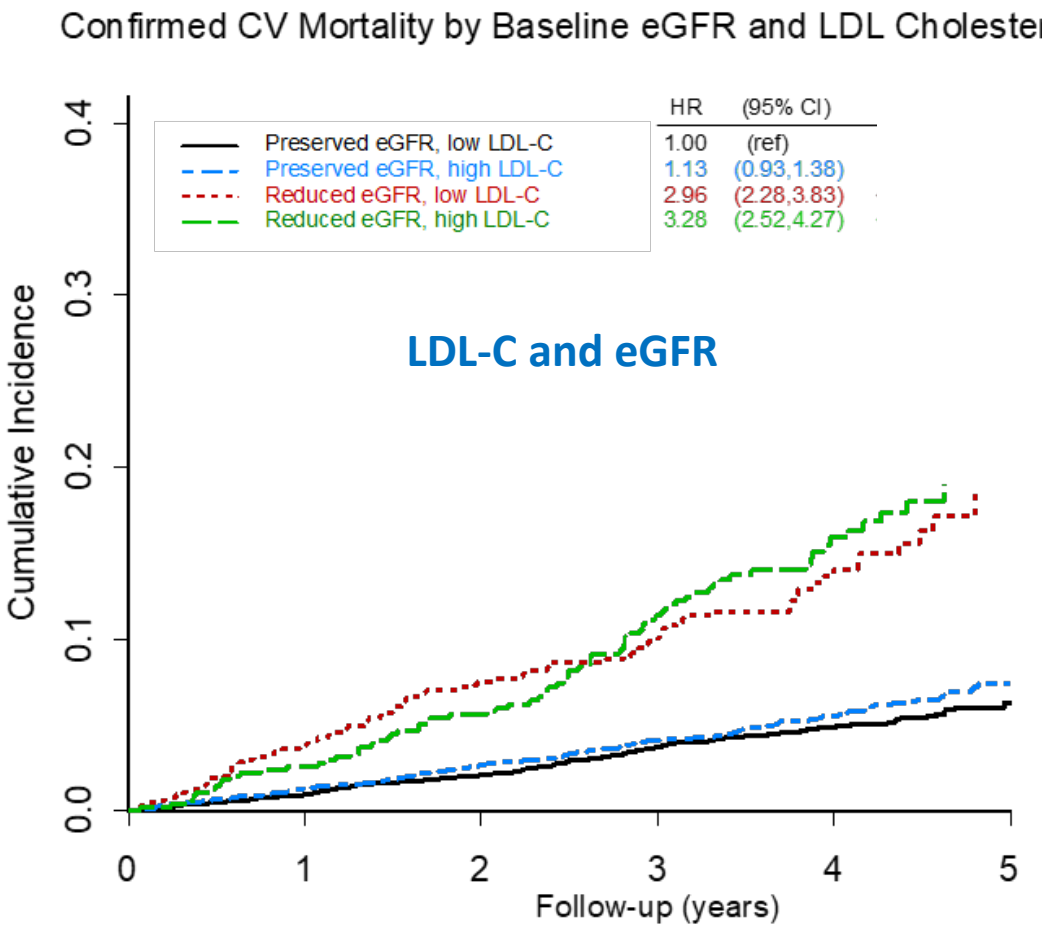
MACE

Impaired Kidney Function

Results III. Joint effects of hsCRP and LDLC on predicting cardiovascular mortality among those with and without chronic kidney disease.



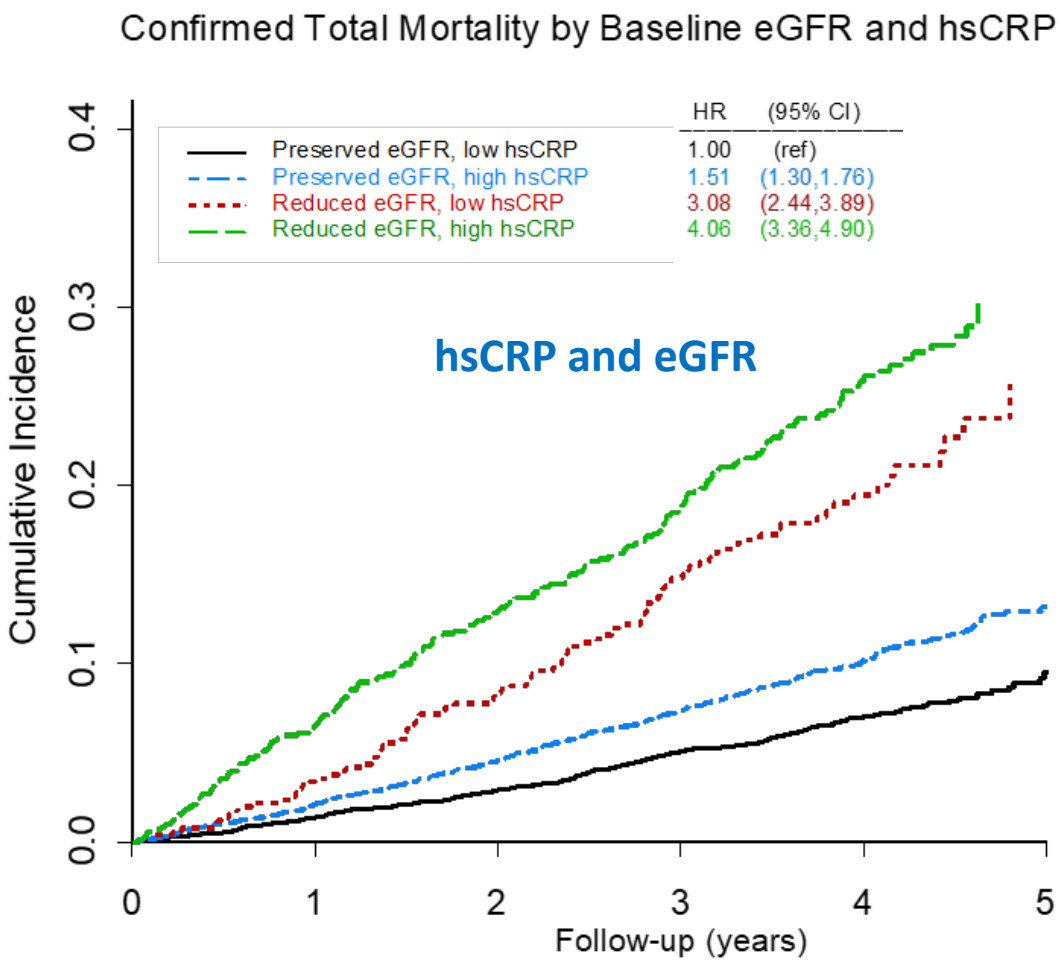
hsCRP and eGFR

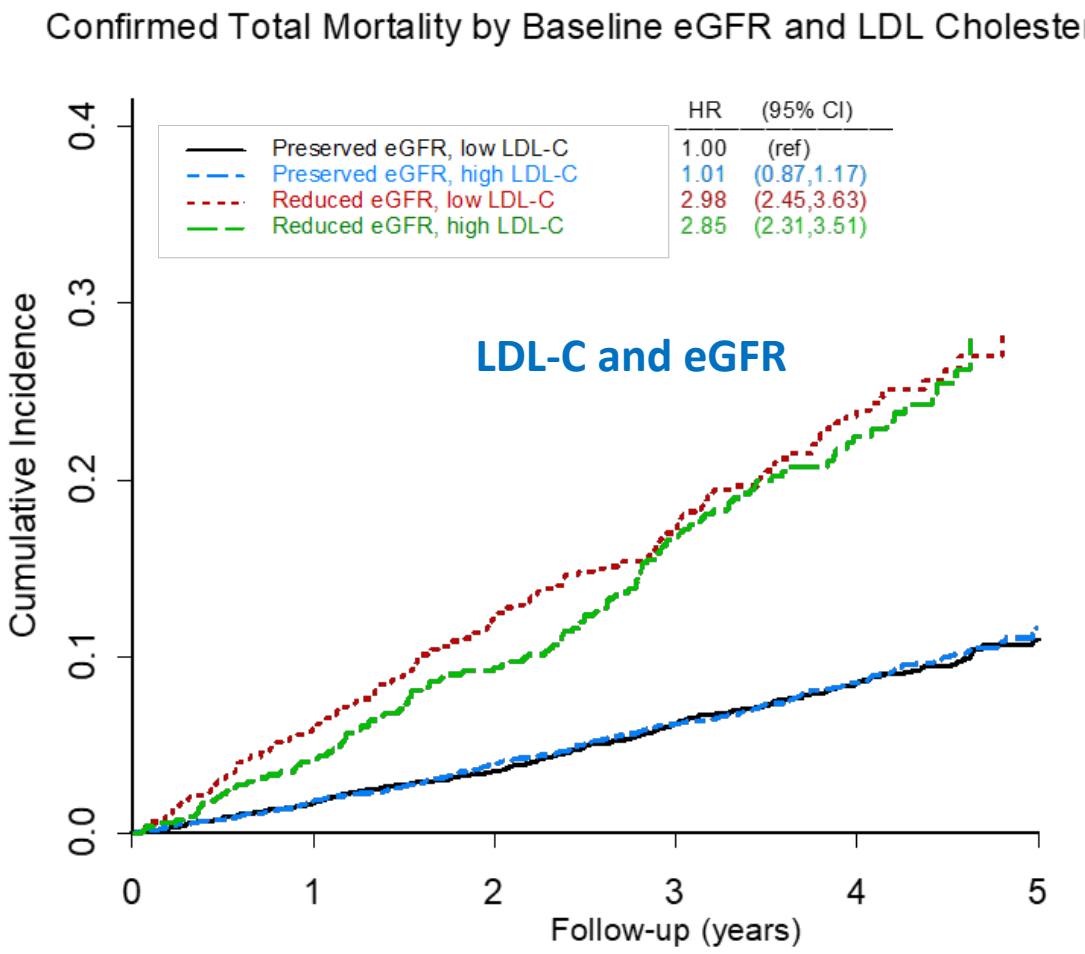


LDL-C and eGFR

Cardiovascular Mortality

Results IV. Joint effects of hsCRP (left) and LDLC (right) on predicting all-cause mortality among those with and without chronic kidney disease.





All-Cause Mortality

Residual Inflammatory Risk and Residual Cholesterol Risk Among Statin Treated Atherosclerosis Patients With and Without Chronic Kidney Disease

Conclusions:

1. Among atherosclerosis patients with impaired kidney function already treated with statin therapy, residual inflammatory risk plays a substantial role in determining the risk of recurrent cardiovascular events.

2. These data have implications for risk stratification of individuals with chronic kidney disease and for the development of novel agents that target inflammatory processes in this high-risk group of patients.

Ziltivekimab Cardiovascular Outcomes Study (ZEUS)

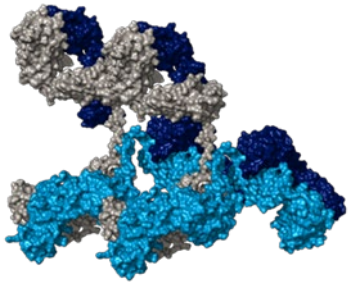
6200 patients
- **ASCVD**
- **CKD stage 3 – 4**
- **hsCRP ≥2mg/L**

IL-6 inhibition with ziltivekimab 15mg SC monthly + usual care

Matching placebo injection SC monthly + usual care

Major Adverse CV Events

Renal Disease Progression

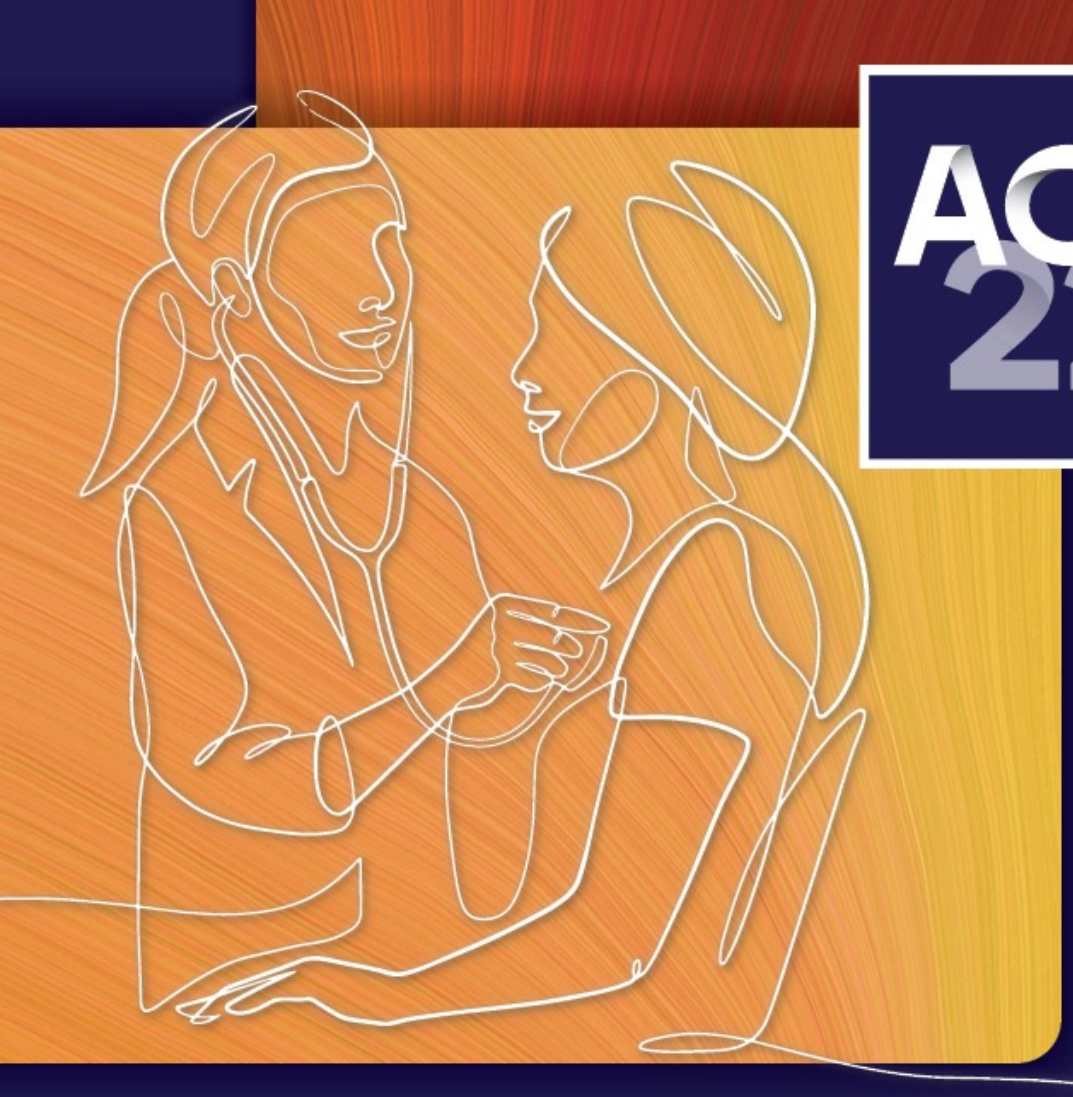


Ziltivekimab : **Narrow spectrum fully human monoclonal antibody targeting the IL-6 ligand that is being developed specifically for atherosclerosis.**

RESCUE Trial : ziltivekimab 15 mg SC monthly
markedly lowered hsCRP, fibrinogen, sPLA2, and Lp(a) without adverse lipid effects

Ridker PM et al for the RESCUE Investigators. Lancet 2021;397:2060-2069

Ridker PM, Rane M. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular Disease Circulation Research 2021;128:1728-1746.



ACC 22

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

NACMI: Trends in Clinical Characteristics, Management Strategies and Outcomes of STEMI Patients with COVID-19

Santiago Garcia, MD
The Christ Hospital, Cincinnati, OH
On Behalf of NACMI Investigators

COVID-19 and STEMI Care:
Direct and Indirect Effects

The Direct Effects

History of Cardiovascular Disease and Risk Factors Associated With Mortality

STEMI With COVID-19 Infection

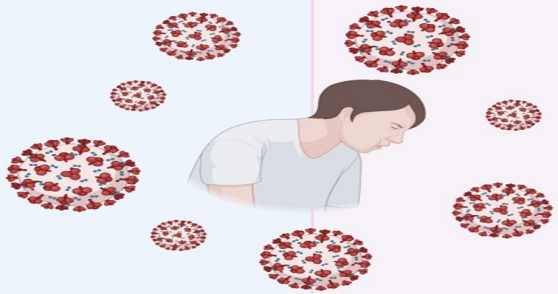
- *20-30% with no culprit lesion*
- *Increase in cardiogenic shock*
- *Increased mortality*

Troponin Elevation Associated With Mechanical Ventilation and Mortality

Up to ~40% elevated troponin

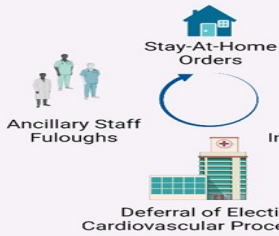
Cardiovascular Complications of COVID-19 Prothrombotic & Proinflammatory

Cardiovascular Effects of COVID-19 Pandemic



The Indirect Effects

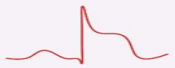
Public Health Restrictions



- *Reduction in diagnostic procedures*
- *Decrease in cardiovascular hospitalizations*
- *Increase in cardiovascular mortality*

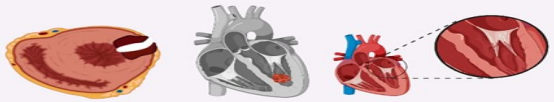
Out-of-Hospital Cardiac Arrest

STEMI Without COVID-19 Infection

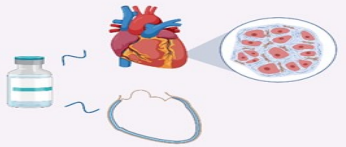


- *Delay to reperfusion*
- *Increase in infarct size and microvascular obstruction*
- *Increase in cardiogenic shock*

Late Mechanical Complications



Vaccine Related Myocarditis and Pericarditis

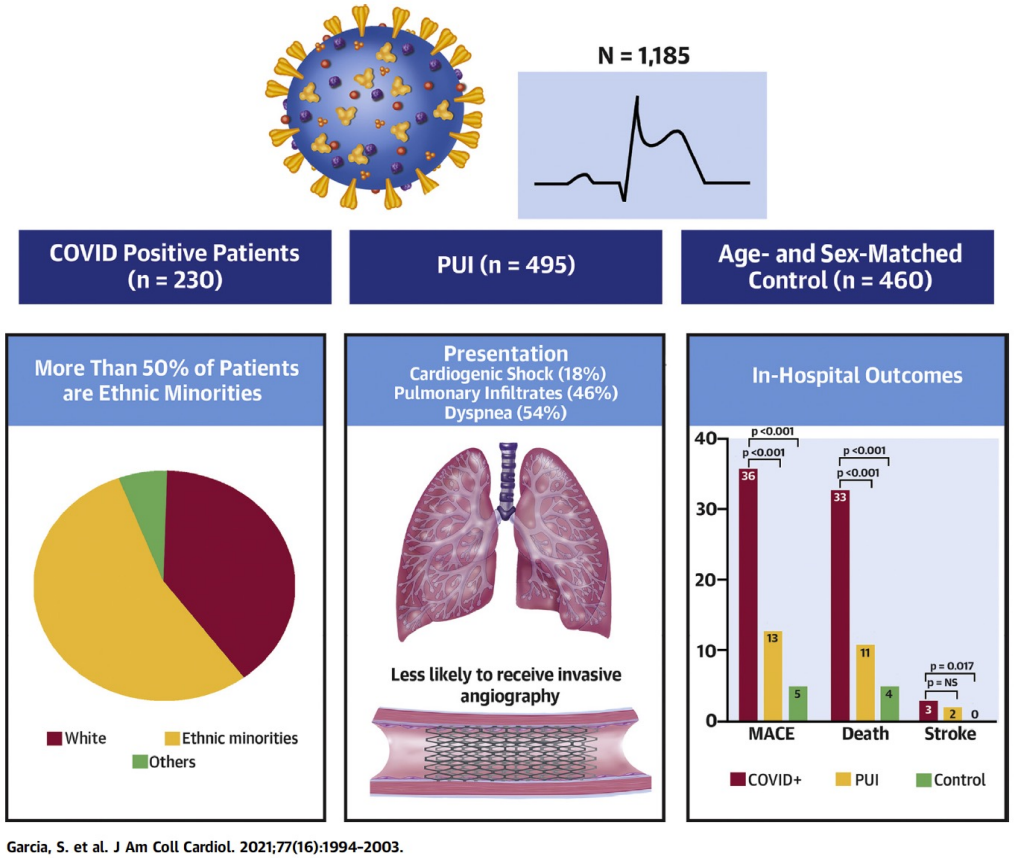


Psychological and Economic Impact

1- *Henry, T. Eur Heart J*, ehab782

Direct Effects of COVID:
STEMI in Patients with COVID-19 Infection

- The risk of myocardial infarction (MI) doubles within 1-2 weeks of receiving a COVID-19 diagnosis
- High-risk subset with distinct clinical features
- Calls to deviate from the standard of care (PPCI) during the pandemic



Garcia, S. et al. J Am Coll Cardiol. 2021;77(16):1994-2003.

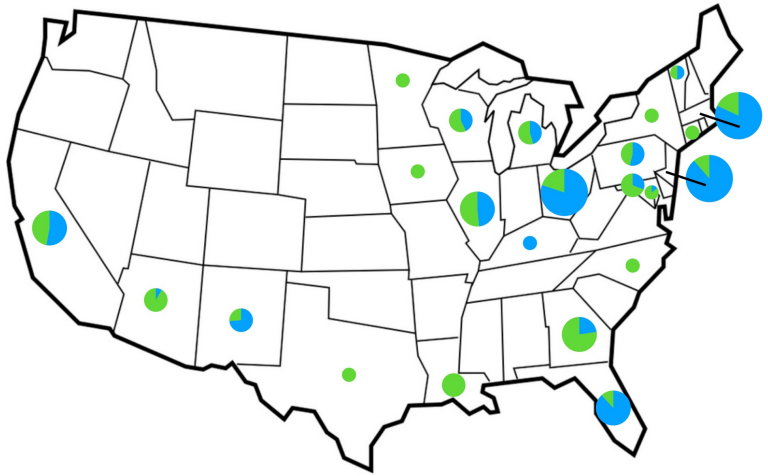
1- Mayo Clin Proc 2021;96:2587-2597

2- Garcia S. JACC 2021; 77 916):1994-2003

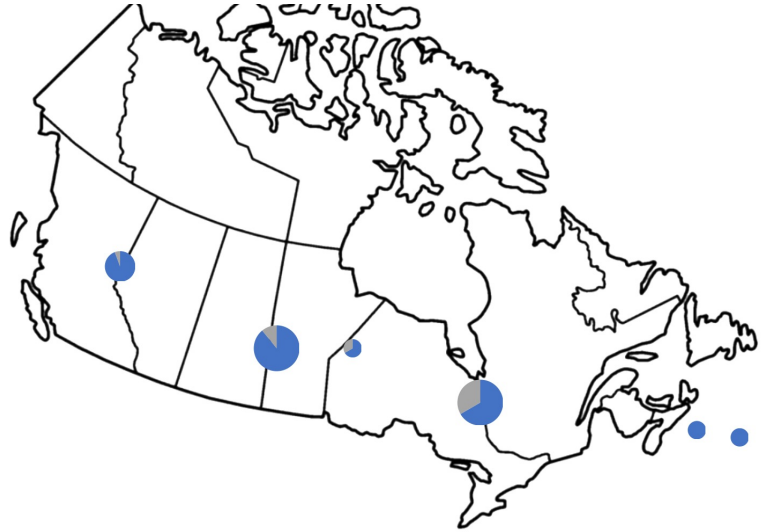
Background

- Despite increased number of COVID-19 cases worldwide, **significant progress has been made** in both disease prevention and management during the course of the pandemic, which has contributed to a **marked reduction in mortality in selected countries**
- Goal: To describe trends in the baseline characteristics, management strategies and outcomes of COVID-19 patients with STEMI during the course of the pandemic

1- Lancet Respir Med 2021;9:397-406.
2- J Hosp Med 2021;16:90-92.
3- Lancet Respir Med 2021;9:322-324.



Methods



- NACMI is a prospective, investigator-initiated, multi-center, observational registry of hospitalized STEMI patients with confirmed or suspected COVID-19 infection in North America
- Broad enrollment criteria without exclusions

Dehghani P et al. Am Heart J 2020;227:11-18.

Methods

Inclusion Criteria

- ***COVID +:*** *A*dult patients (≥18 years) with 1) *ST-segment elevation* in at least 2 contiguous leads (or new-onset left bundle branch block), 2) a *clinical correlate of myocardial ischemia* (e.g., chest pain, dyspnea, cardiac arrest, shock, mechanical ventilation) and 3) *confirmed COVID +* by any commercially available test during, or 4 weeks before, the index STEMI hospitalization.
- ***PUIs:*** *A*dult patients with STEMI who were suspected positive on presentation but subsequently *tested negative for COVID-19 infection* (person under investigation or PUI). The definition of PUI was left to the discretion of local hospitals but in general included a combination of possible COVID signs and symptoms (fever or respiratory symptoms such as cough, shortness of breath, sore throat), or exposure to a confirmed case or cluster of suspected COVID-19 cases.

Methods

Outcomes

- **Primary:** In-hospital mortality
- Secondary: stroke, composite of death, stroke or reinfarction

Comparison

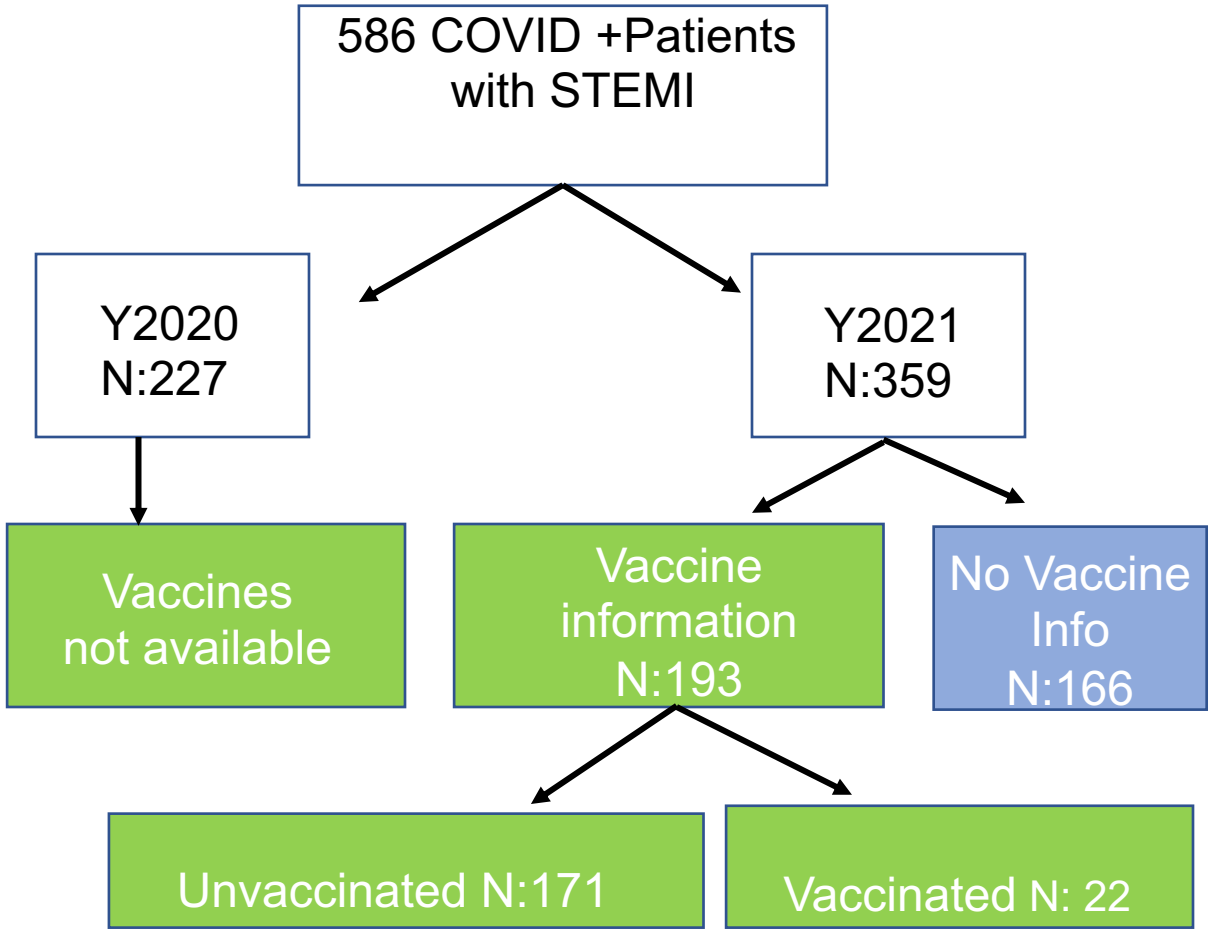
- COVID+ patients were divided into two groups according to the year of the STEMI presentation during the pandemic, i.e. **Y2020** group (3/1/2020 - 12/31/2020) and **Y2021** group (1/1/2021 - 12/31/2021)
- These periods coincided with the ***commercial introduction of vaccines against COVID-19 in North America.***

Statistics

- Demographic, clinical, and outcome variables were compared between the groups using Pearson's chi-squared or Fisher's exact test for categorical data and Student's t-test or Wilcoxon rank-sum test for continuous variables, as appropriate.
- The relative risk of death for Y2021 vs Y2020 group is estimated from a multivariate robust Poisson regression analysis with a canonical log-link and robust sandwich estimator of variance to allow for overdispersion in the data.
- Model covariates include age, BMI, gender, race, diabetes, abnormal chest X-ray findings, and shock pre-PCI.
- Age originally collected as a five-category variable is dichotomized as < 66 or ≥ 66 years; and BMI categories are defined overweight/obese or not per CDC definition.
- A proxy comorbidity index is defined to capture the pre-existing cardiovascular diseases/conditions as follows: a sum of indicators of hypertension and history of PCI, MI, CABG, stroke, or CHF for each patient is dichotomized to index those with three or more pre-existing conditions

Vaccines: 74% overall, 54% of Y2021patients with vaccine information

- NACMI was designed in early 2020 prior to the commercialization of vaccines against COVID-19
- Vaccine status was not routinely captured in the registry
- However, once vaccines became commercially available in North America in 2021 the original protocol was amended to include immunization status including timing and type
- The protocol amendment was approved by 20 enrolling sites at the time of this publication



Results

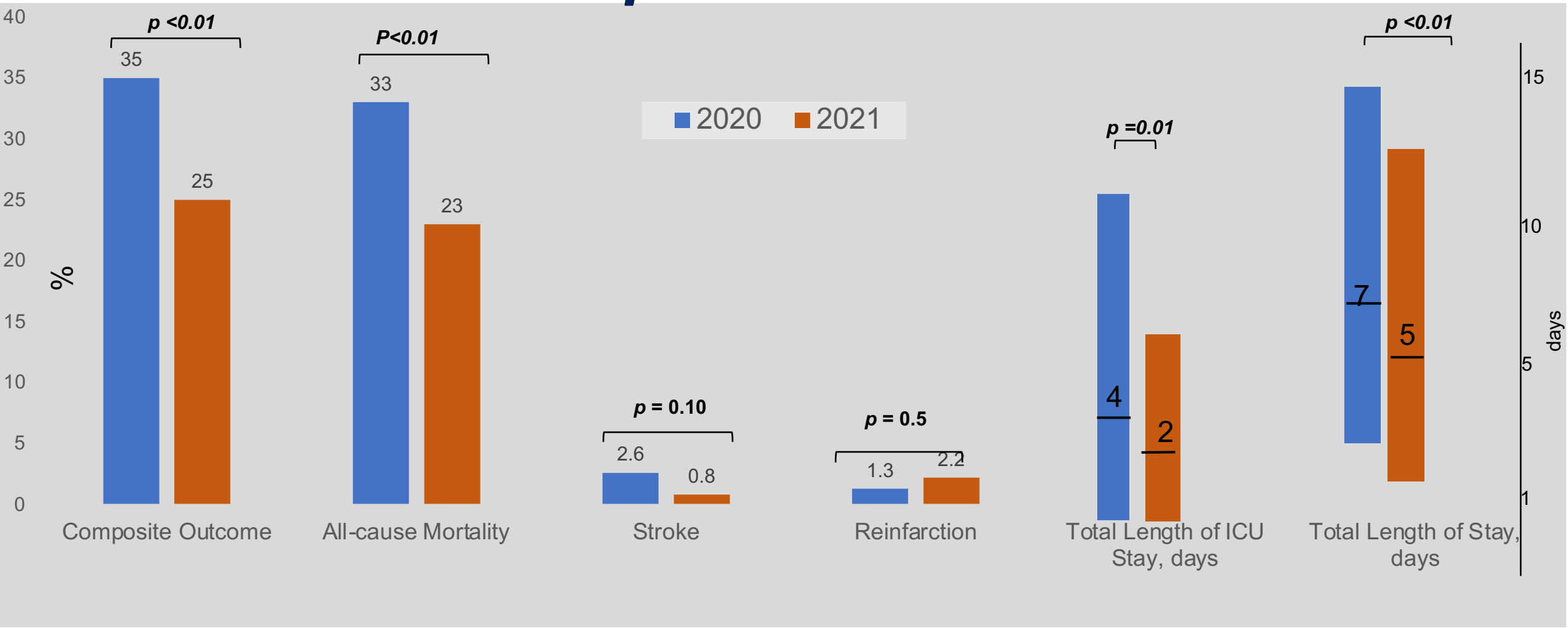
Baseline Characteristics	Y2020 n = 227	Y2021 n = 359	p-value
Age > 55 years	175 (77)	261 (73)	0.3
Male	163 (72)	268 (75)	0.4
History of CAD	51 (24)	88 (28)	0.3
Non-Caucasian	137 (61)	142 (42)	<0.001
Dyslipidemia	98 (45)	145 (46)	0.9
Diabetes Mellitus	102 (46)	135 (42)	0.4
BMI (Kg/m^2) - mean ± SD	29 ± 8	27 ± 10	0.5
Hypertension	165 (74)	223 (65)	0.025
History of Heart Failure	33 (16)	51 (16)	0.9
Symptoms at Presentation			
Dyspnea	126 (56)	152 (42)	0.002
Chest pain	115 (51)	212 (59)	0.046
Syncope	6 (2.6)	16 (4.5)	0.3
Infiltrates on Chest X-ray	106 (47)	120 (33)	0.001
Cardiac arrest pre-PCI	23 (11)	24 (7.9)	0.2
Shock pre-PCI	37 (18)	38 (13)	0.079
Ejection Fraction	43 (35, 55)	45 (34, 55)	0.5
In-House presentation of MI	13 (5.7)	26 (7.4)	0.4

Utilization of Invasive Angiography and Coronary Revascularization

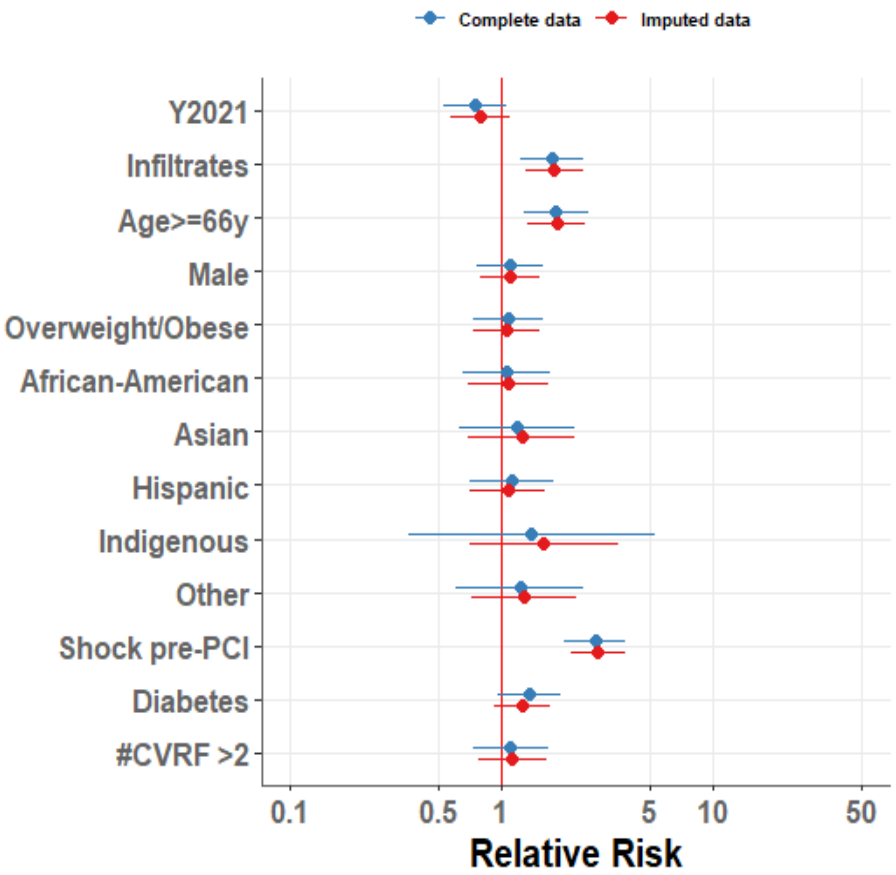
Variable	Y2020 n = 227	Y2021 n = 359	p-value[1]
No angiogram	52 (23)	49 (14)	0.004
Patients undergoing invasive angiography, n = 485			
Reperfusion strategy	n = 175	n =310	0.7
CABG	3 (1.7)	5 (1.6)	
Facilitated/Rescue PCI	7 (4.0)	11 (3.5)	
Medical therapy	34 (19)	78 (25)	
Primary PCI	125 (71)	206 (66)	
Thrombolytics	6 (3.4)	10 (3.2)	

Results

In-Hospital Outcomes



Results (Cont'd)

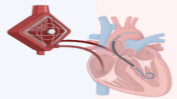
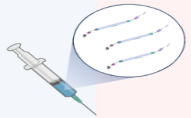


- Risk of in-hospital mortality 25% lower (95% CI: -47-5, p=0.01) in Y2021 relative to Y2020
- Risk 1.7 (95% CI:1.2, 2.4, p=0.002) times higher if infiltrates were observed on X-Ray and nearly three times higher (95% CI:1.9-3.9, p<0.001) if cardiogenic shock was present
- Risk also higher for patients ≥66 years of age

Vaccine Effect (Y2021)

	Unvaccinated, n = 171	Vaccinated, n = 22	p-value[1]
Age < 66y	104 (61)	12 (55)	0.572
Overweight / Obese	128 (78)	16 (89)	0.372
CVRF <3	137 (80)	19 (86)	0.579
Dyspnea	79 (46)	6 (27)	0.092
Chest Pain	107 (63)	15 (68)	0.608
Syncope	6(3.5)	1 (4.5)	0.577
Infiltrates on Chest X-Ray	64 (37)	4 (18)	0.075
Cardiac arrest pre-PCI	8 (5.4)	1 (5.0)	1.0
Shock pre-PCI	20 (14)	2 (10)	1.0
Ejection Fraction	45 (34, 55)	45 (44, 54)	0.404
In-House presentation of MI	19 (11)	0	0.137
Clinical Outcomes			
Mortality	37 (22)	0 (0)	0.009
Stroke	1 (0.6)	0 (0)	1.0
Reinfarction	3 (1.8)	1. (4.5)	0.386
Composite end-point	38 (22)	1 (4.5)	0.052

Trends In STEMI Patients With Infection

	2020		2021
Non-Caucasian	61%		42%
Symptom/Dyspnea	56%		42%
Infiltrates On Chest X-Ray	47%		33%
Cardiogenic Shock	18%		13%
Covid-19 Vaccination	0%		11%
In-Hospital Mortality	33%		23%

Simultaneous Publication in JACC

Acknowledgements

- NACMI received financial support from ACC, Saskatchewan Health Research Foundation (SHRF), Medtronic and Abbott Vascular
- Minneapolis Heart Institute Foundation (MHIF) data coordinating site
- 64 enrolling sites without compensation and in the midst of a pandemic that significantly affected biomedical research

Conclusions

- In-hospital mortality decreased 25% in Y2021
- Possible mediators: lower risk profile of patients, more typical ischemic symptoms, less cardiogenic shock and pulmonary involvement
- Vaccinated patients less likely to develop respiratory complications, none of them expired
- In contrast, mortality remains high (22%) for unvaccinated patients
- Despite logistical challenges, PCI remains dominant revascularization modality, 2/3 D2B time ≤ 90 minutes
- **In summary, the clinical profile, management and outcomes of STEMI patients with COVID-19 infection is evolving towards that of STEMI patients prior to the pandemic although mortality remains high for unvaccinated patients**

A Single Ascending Dose Study of an siRNA Targeting Lipoprotein(a)

Steven E. Nissen MD MACC
for the APOLLO Study Investigators

Disclosure

Consulting: Many pharmaceutical companies

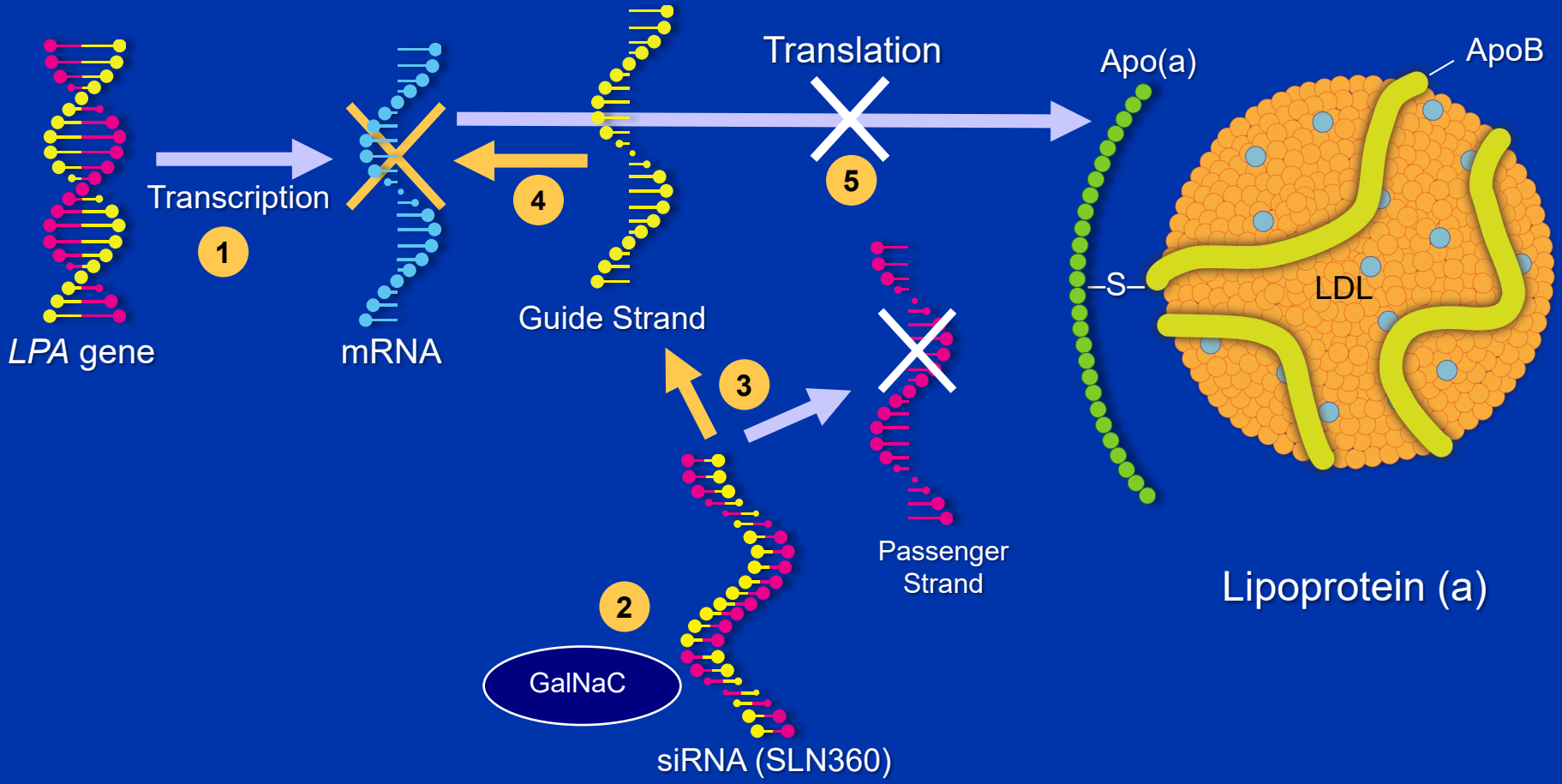
Clinical Trials: AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Esperion, Medtronic, Novartis, Silence Therapeutics, and Pfizer.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

Background

- Lipoprotein(a) is an important risk factor for ASCVD and aortic stenosis with no treatments approved by regulatory authorities.
- The *LPA* gene encodes for apolipoprotein(a), a dominant, rate-limiting component in the hepatic synthesis of Lp(a).
- An siRNA is a double-stranded RNA designed to degrade a specific mRNA to suppress the translation of a target gene.
- The Phase 1 APOLLO trial examined the tolerability and Lp(a) lowering effects of SLN360 (Silence Therapeutics, London, UK) an siRNA targeting mRNA specific for the *LPA* gene.

Mechanism of Action of SLN360 in Lowering Lp(a)

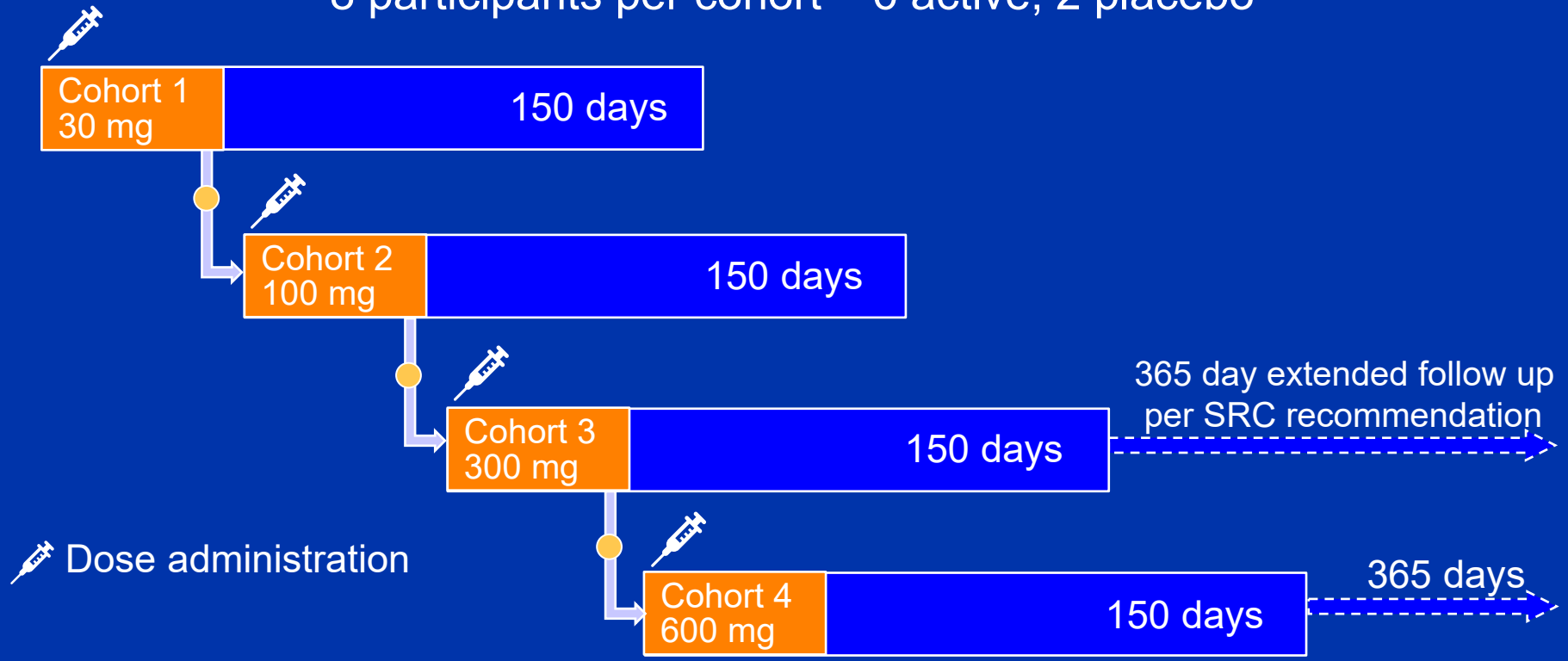


Study Design

- Adults ≥18 years in age without known ASCVD and an Lp(a) concentration ≥150 nmol/L.
- Single dose cohorts randomized to SLN360 (30 mg, 100 mg, 300 mg or 600 mg) or placebo given subcutaneously.
- Participants monitored in a Clinical Research Unit for 24 hours following dose administration.
- Visits at 7, 14, 30, 45, 60, 90 and 150 days following administration.

Study Schematic: Single Ascending Dose Study

8 participants per cohort – 6 active, 2 placebo



- Safety Review Committee (SRC) reviewed data for a minimum of 4 participants on SLN360

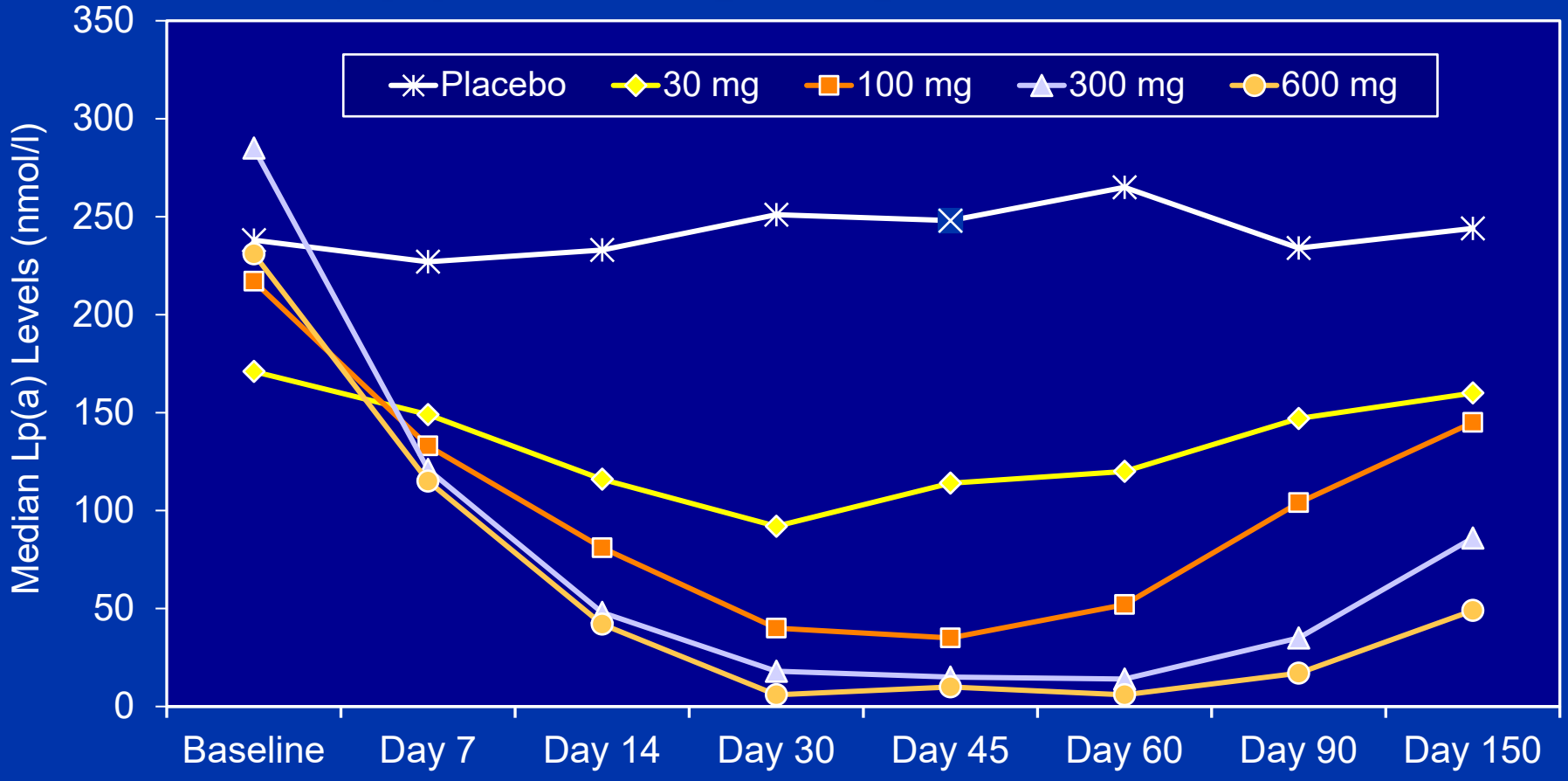
Outcomes

- *Safety:*
  - Vital signs, physical examination, ECG, lab chemistries
  - Treatment emergent adverse events – AE's of special interest and any dose-limiting toxicity.
- *Efficacy:*
  - Primary: Effect on lipoprotein(a) concentration from baseline to 150 days.
  - Effects on LDL-C, apoB, oxidized LDL, inflammatory markers, plasminogen and pharmacokinetics.

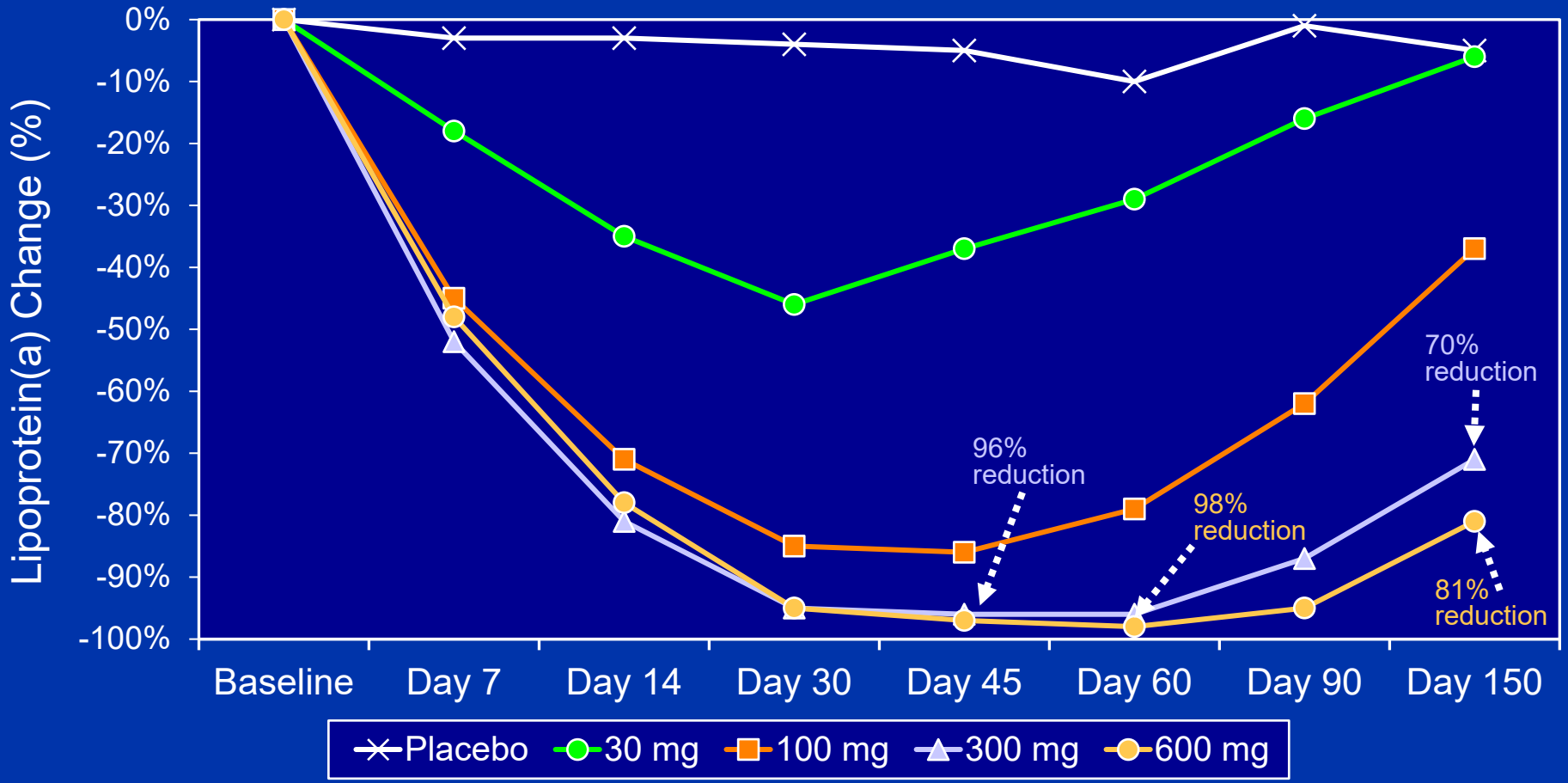
Baseline Characteristics

	All Participants (n=32)	Placebo (n=8)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Age (years)	**49.6**	52.9	45.5	46.3	58.7	43.7
Male (%)	**47**	25	67	67	33	50
Mean BMI, kg/m^2	**27**	25	26	29	29	27
Median Lp(a), nmol/L	**224**	238	171	217	285	231
Mean LDL-C, mg/dL	**108**	99	113	121	100	108
Mean ApoB, mg/dL	**85**	81	83	94	89	81

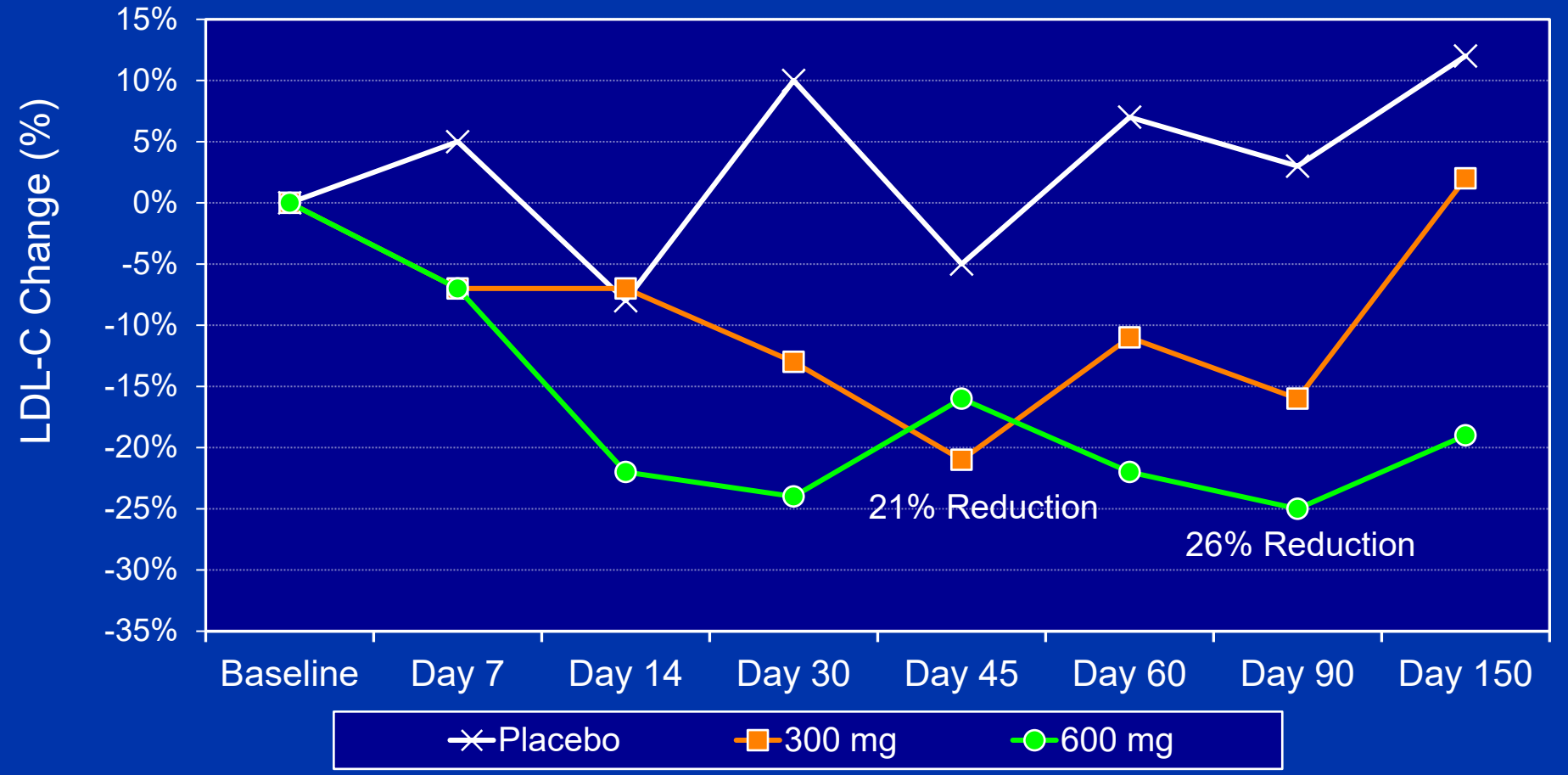
Median Lp(a) following Single Doses of SLN360



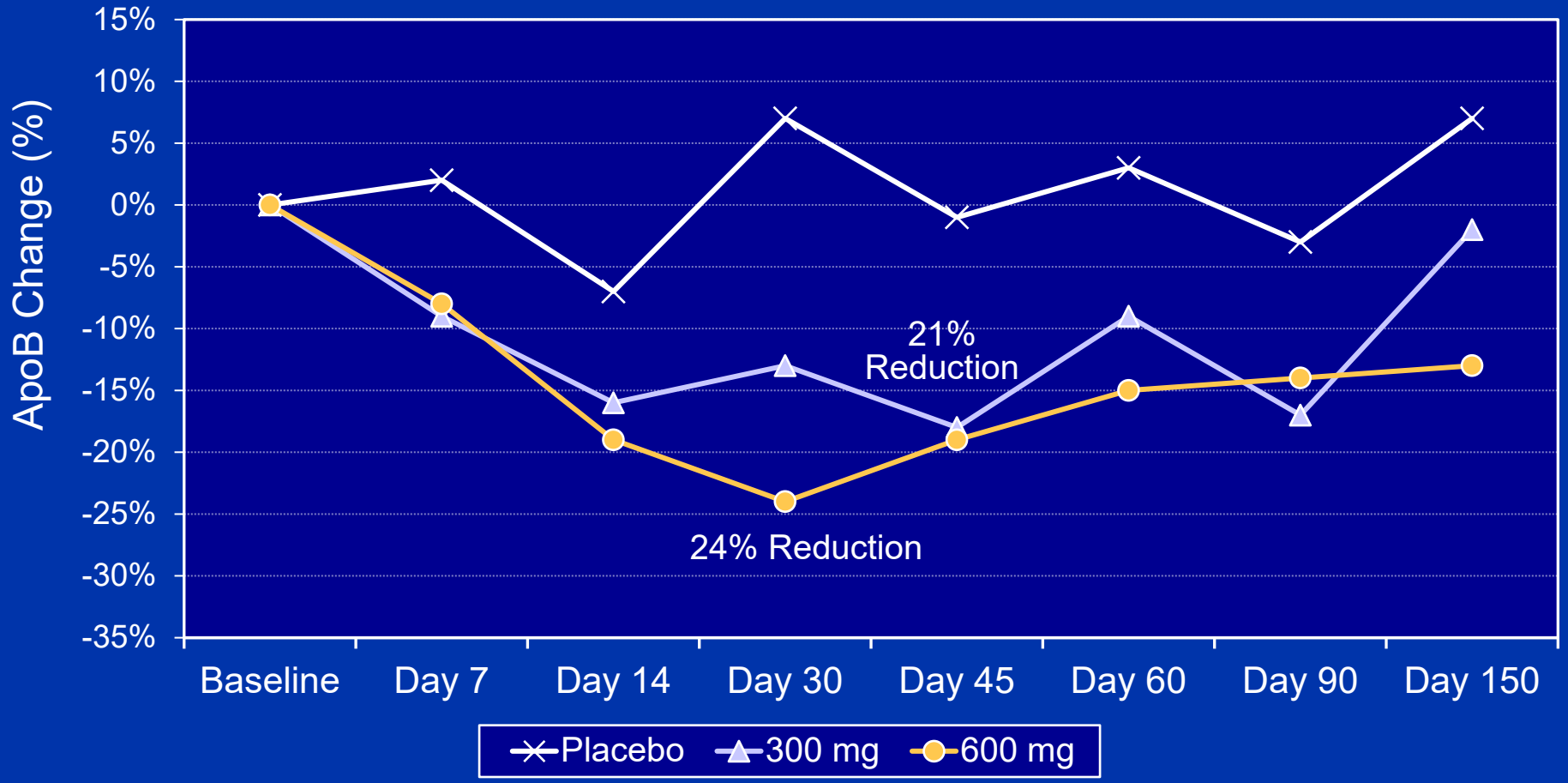
Median Percent Lowering of Lipoprotein(a)



Mean Percent Reduction in LDL-C for Two Highest Doses



Mean Percent Reduction in ApoB for Two Highest Doses



Safety: Treatment Emergent Adverse Events

	All (n=32)	Placebo (n=8)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Treatment emergent adverse events occurring in more than 3 participants, n (%)						
Headache	9 (28)	1 (13)	2 (33)	1 (17)	0 (0)	5 (83)
Diarrhea	3 (9)	1 (13)	1 (17)	0 (0)	0 (0)	1 (17)
Arthralgia	3 (9)	0 (0)	1 (17)	0 (0)	1 (17)	1 (17)
Neutrophil count increased	3 (9)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)
C-reactive protein increased	4 (32)	0 (0)	0 (0)	0 (0)	0 (0)	4 (67)
Serious Adverse Events, n (%)	1 (3)	0 (0)	1 (17)*	0 (0)	0 (0)	0 (0)

* A single participant experienced 2 SAE episodes, unrelated to SLN360

Effect on Liver Enzymes and Injection Site Reactions

	All (n=32)	Placebo (n=8)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Liver Enzymes, n (%)						
ALT > 3x ULN	1(3)*	0 (0)	1 (17)^	0 (0)	0 (0)	0 (0)
AST > 3x ULN	1(3)*	0 (0)	1 (17)^	0 (0)	0 (0)	0 (0)
ALP† >2x ULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
*Injection site reactions, n (%)						
Grade 1	18 (56)	1 (13)	5 (83)	6 (100)	4 (67)	2 (33)
Grade 2	5 (16)	0 (0)	0 (0)	0 (0)	1 (17)	4 (67)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Graded using the Common Terminology Criteria for Adverse Events †Alkaline phosphatase ^Same individual, single time point

Limitations

- This was a small, first-in-man Phase 1 trial enrolling only 32 participants.
- Safety cannot be comprehensively assessed in a trial of this size and duration.
- A population without known cardiovascular disease was selected for study.
- Single doses administered - effects of multiple doses uncertain, although a multidose study is underway.

JAMA | Original Investigation

Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Levels

Steven E. Nissen, MD; Kathy Wolski, MPH; Craig Balog, BS; Daniel I. Swerdlow, MD, PhD; Alison C. Scrimgeour, MSc; Curtis Rambaran, MD; Rosamund J. Wilson, PhD; Malcom Boyce, MD; Kausik K. Ray, MD; Leslie Cho, MD; Gerald F. Watts, MD, PhD; Michael Koren, MD; Traci Turner, MD; Erik S. Stroes, MD, PhD; Carrie Melgaard, MS; Giles V. Campion, MD, PhD

IMPORTANCE Lipoprotein(a) (Lp[a]) is an important risk factor for atherothrombotic cardiovascular disease and aortic stenosis, for which there are no treatments approved by regulatory authorities.

OBJECTIVES To assess adverse events and tolerability of a short interfering RNA (siRNA) designed to reduce hepatic production of apolipoprotein(a) and to assess associated changes in plasma concentrations of Lp(a) at different doses.

DESIGN, SETTING, AND PARTICIPANTS A single ascending dose study of SLN360, an siRNA targeting apolipoprotein(a) synthesis conducted at 5 clinical research unit sites located in the

+ Visual Abstract
+ Editorial
+ Supplemental content

Conclusions

- Subcutaneous injection of an siRNA (SLN360) targeting mRNA for the *LPA* gene lowered lipoprotein(a) up to 98%.
- >70% and >80% reductions in Lp(a) persisted for 150 days after the 300 mg and 600 mg doses.
- The highest doses reduced LDL-C and ApoB by 20-30%.
- There were no major safety issues, although low-grade, transient, dose-dependent injection site reactions occurred.
- These findings support further development of this therapy.

A Final Thought

Historically, elevated lipoprotein(a) has been considered an untreatable abnormality. The development of therapies targeting mRNA has made possible significant lowering of Lp(a). Whether these reductions can impact on the incidence of ASCVD events or prevent progression of aortic stenosis remains to be determined, but optimism is warranted.

Supermarket and Web-Based Intervention Targeting Nutrition

"SuperWIN"

A Randomized, Parallel Assignment, Active Control, Efficacy Trial

Dylan L. Steen M.D., M.S., Robert N. Helsley, Ph.D., Deepak L. Bhatt, M.D., M.P.H., Eileen C. King, Ph.D., Suzanne S. Summer, Ph.D., R.D.N., Matthew Fenchel, M.S., Brian E. Saelens, Ph.D., Mark H. Eckman, M.D., M.S., Sarah C. Couch, Ph.D., R.D.N.

UC CINCINNATI

Cincinnati Children's

Disclosures

Dr. Dylan L. Steen discloses the following relationships:

- Consultant: Sanofi
- CEO/Cofounder: High Enroll, LLC

SuperWIN received partial funding and other support (e.g., clinic space and equipment, study dietitians, and purchasing data) from The Kroger Company.

Background

2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association

Alice H. Lichtenstein, DSc, FAHA, Chair*; Lawrence J. Appel, MD, MPH, FAHA, Vice Chair*; Maya Vadiveloo, PhD, RD, FAHA, Vice Chair; Frank B. Hu, MD, PhD, FAHA; Penny M. Kris-Etherton, PhD, RD, FAHA; Casey M. Rebholz, PhD, MS, MNSP, MPH, FAHA; Frank M. Sacks, MD, FAHA; Anne N. Thorndike, MD, MPH, FAHA; Linda Van Horn, PhD, RD, FAHA; Judith Wylie-Rosett, PhD, RD, FAHA; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; and Stroke Council

- Guidelines continue to recommend heart-healthy dietary patterns, like the Dietary Approaches to Stop Hypertension (DASH) Diet.
- Public adherence to healthy dietary patterns remains low.

Innovation is needed….

versus

Background

AHA SCIENCE ADVISORY

Innovation to Create a Healthy and Sustainable Food System

A Science Advisory From the American Heart Association

2019 Advisory calls for "immediate action" for more sponsored research with retailers (e.g. supermarkets), research on online shopping to promote healthier purchases, and research on nutrition and health applications.

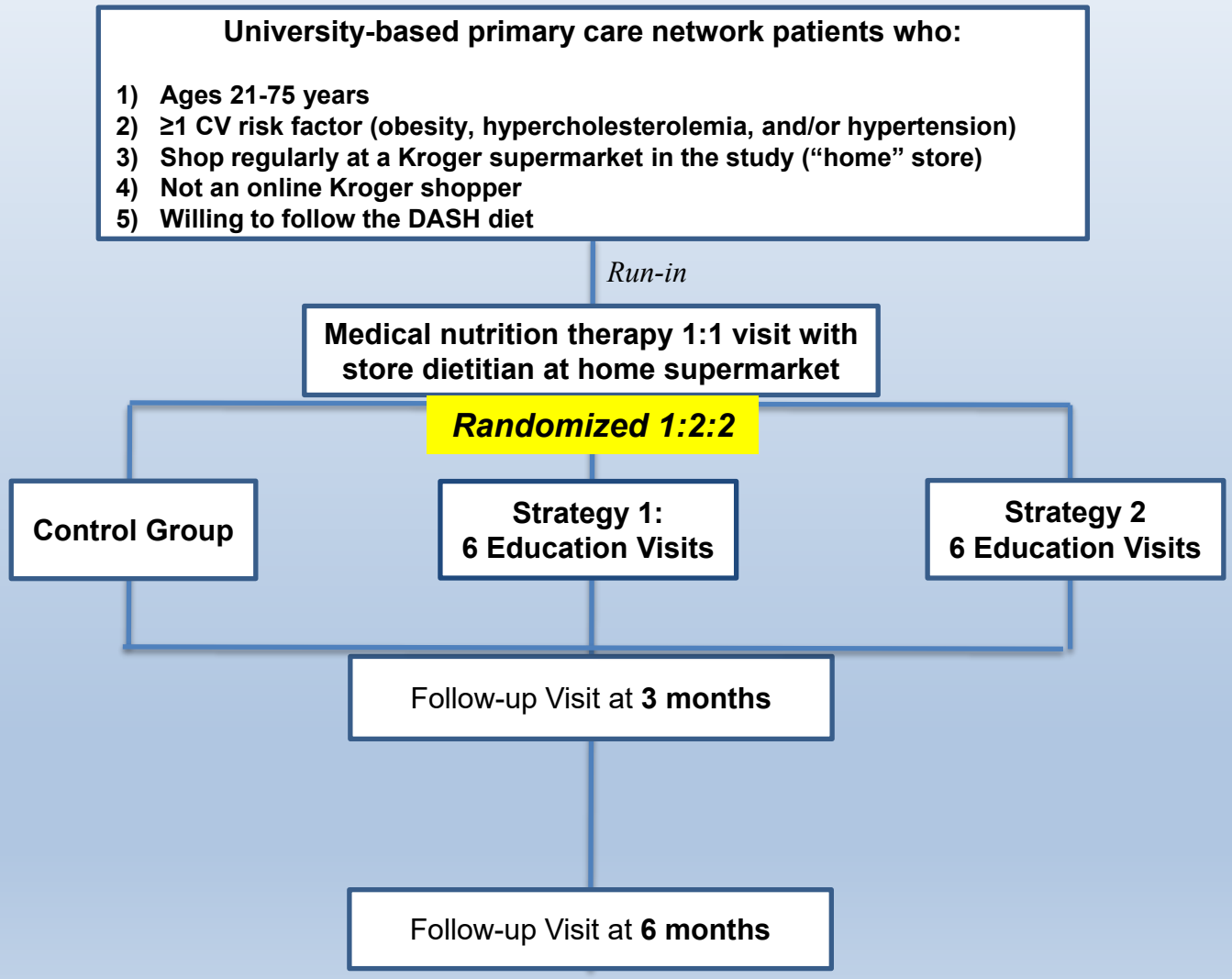
In a broader context, delivery of healthcare beyond hospitals and clinics in needed. Key elements:

- Access, Convenience, Engagement, and Effectiveness
- Testing Platforms and Rigorous Studies
- New Industry Partners

Hospitals

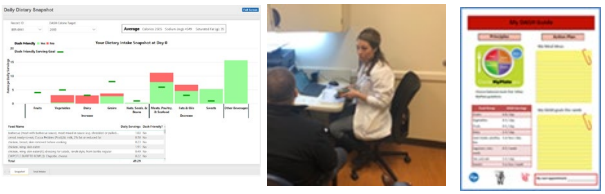
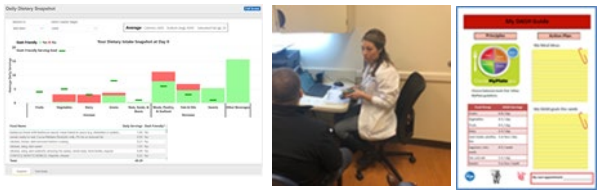
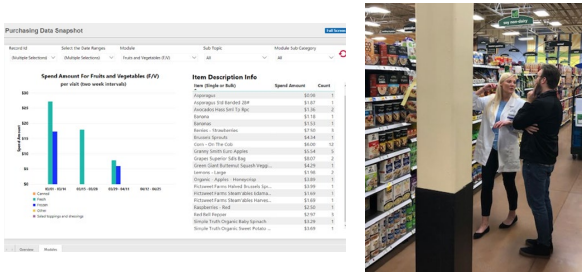
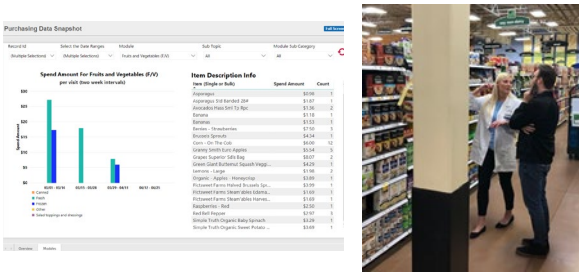
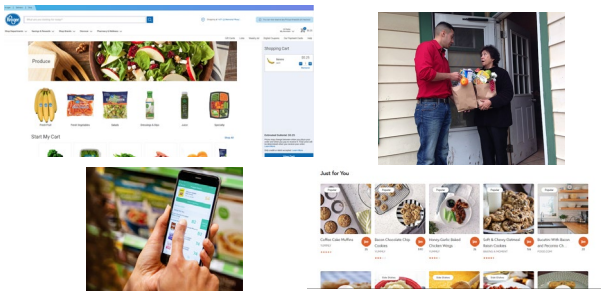
Clinics

SuperWIN Study Design

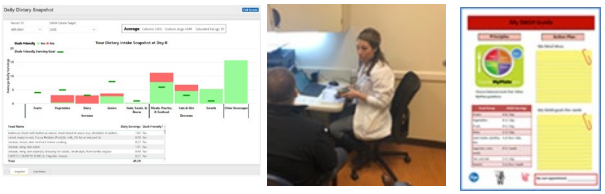
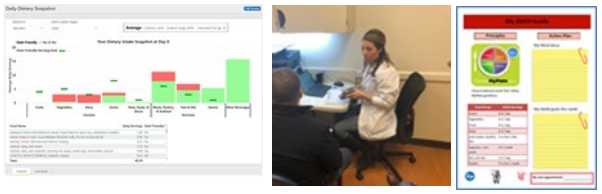
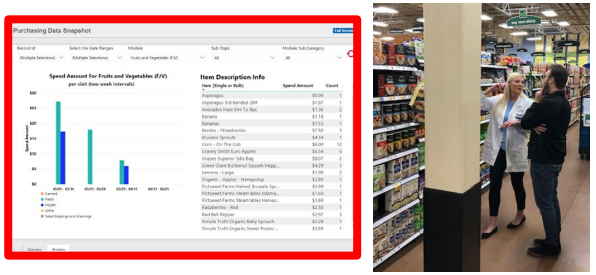
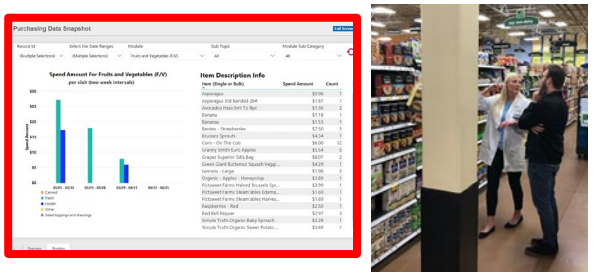
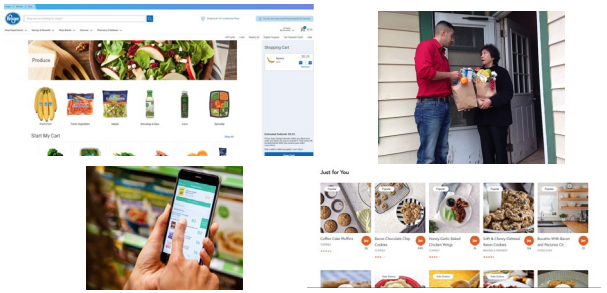


Couch SC, Helsley RN, Siegel FU, et al, Steen DL, AHJ, 2022

Dietary Education

Control	Strategy 1	Strategy 2
Medical Nutrition Therapy (30min) 	Medical Nutrition Therapy (30min) 	Medical Nutrition Therapy (30min) 
Randomized 1:2:2		
	Purchasing data-guided, “in the aisles” education (6 sessions- 60min each) 	Purchasing data-guided, “in the aisles” education (6 sessions- 60min each) 
		Stepwise introduction and training on technologies (e.g., online shopping) 

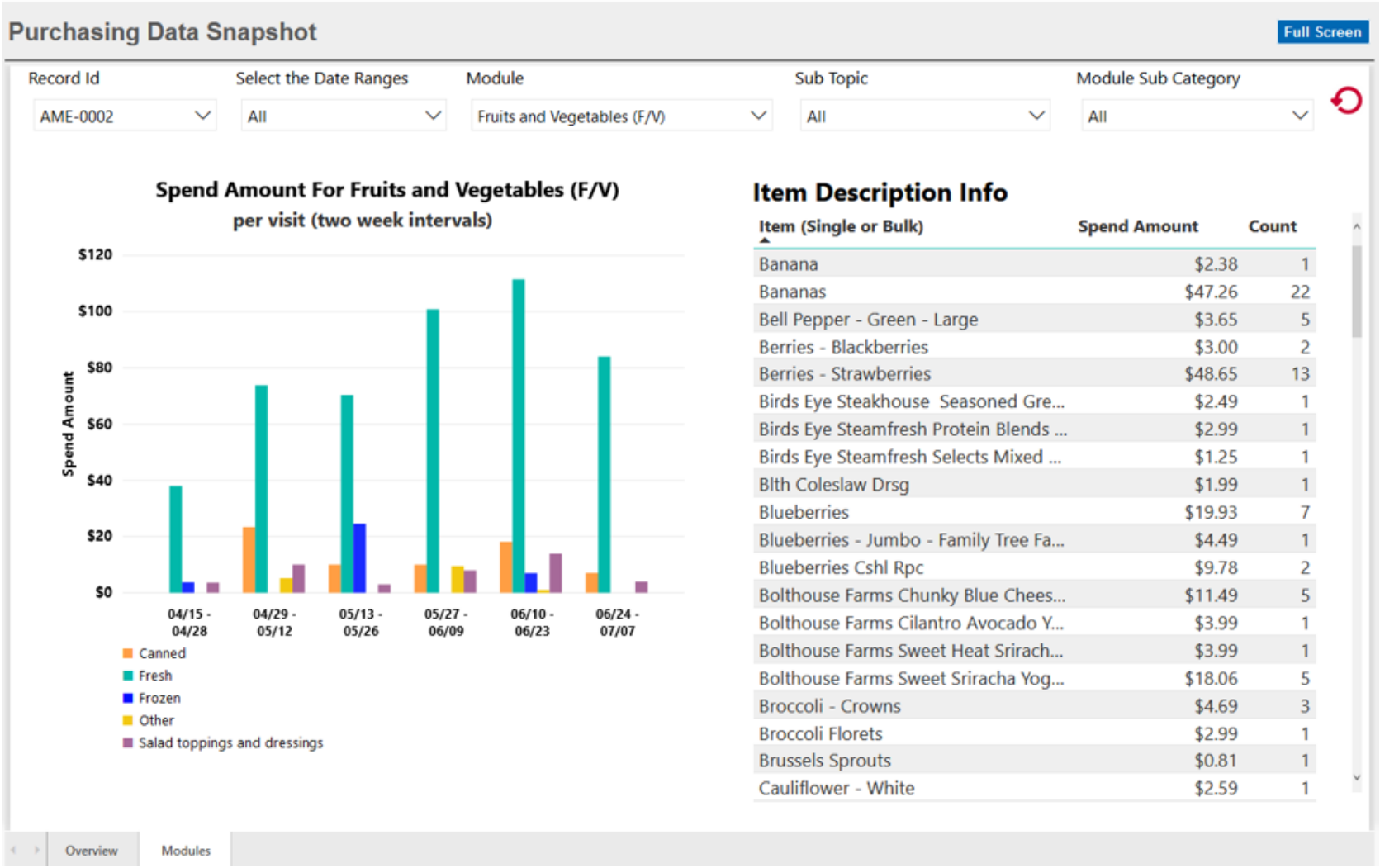
Dietary Education

Control	Strategy 1	Strategy 2
Medical Nutrition Therapy (30min) 	Medical Nutrition Therapy (30min) 	Medical Nutrition Therapy (30min) 
Randomized 1:2:2		
	Purchasing data-guided, “in the aisles” education (6 sessions- 60min each) 	Purchasing data-guided, “in the aisles” education (6 sessions- 60min each) 
		Stepwise introduction and training on technologies (e.g., online shopping) 

Individualized Purchase Review

(Both Strategies 1 and 2)

Example



Hypothesis Testing

∆ DASH score (baseline to 3 months):

1) <u>Strategies 1 and 2</u> versus <u>Control</u>

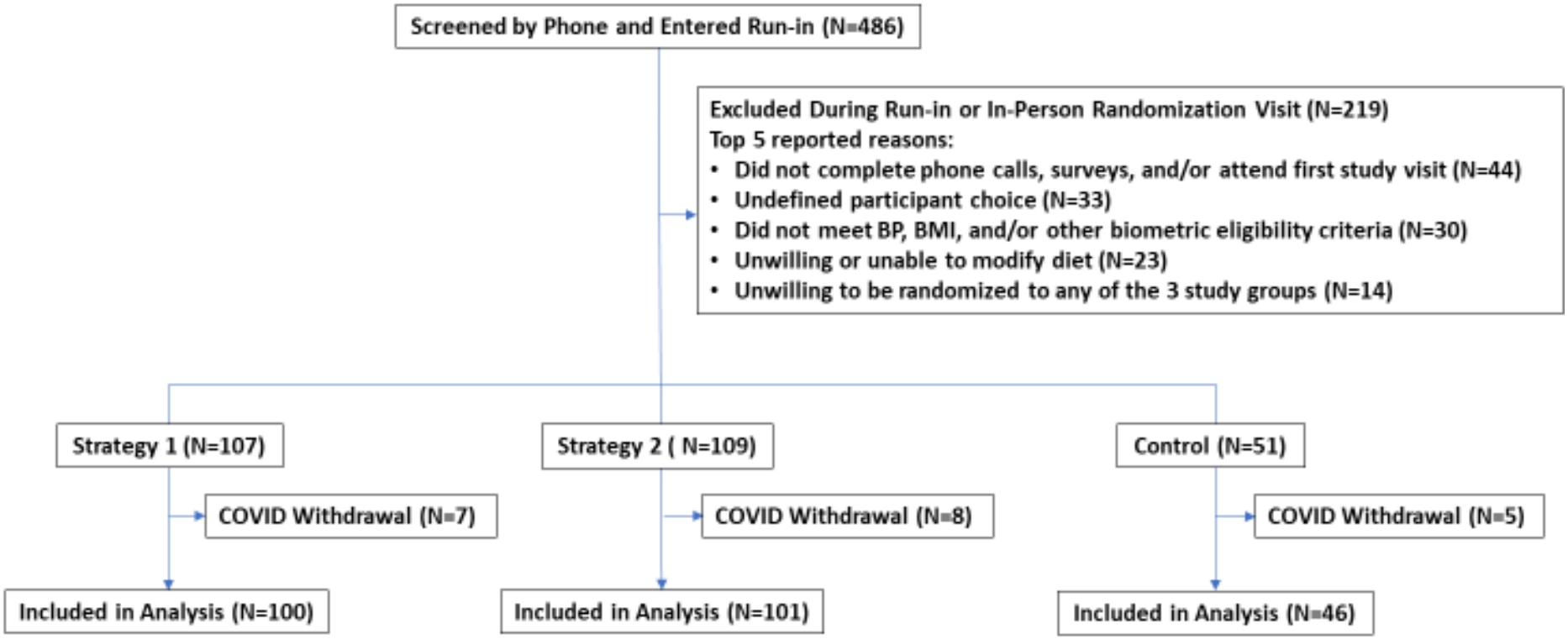
if p <0.05, then

2) <u>Strategy 2</u> versus <u>Strategy 1</u>

<u>DASH score:</u>

- Range 0-90.
- Higher is better.
- Calculated from raw dietary intake data.

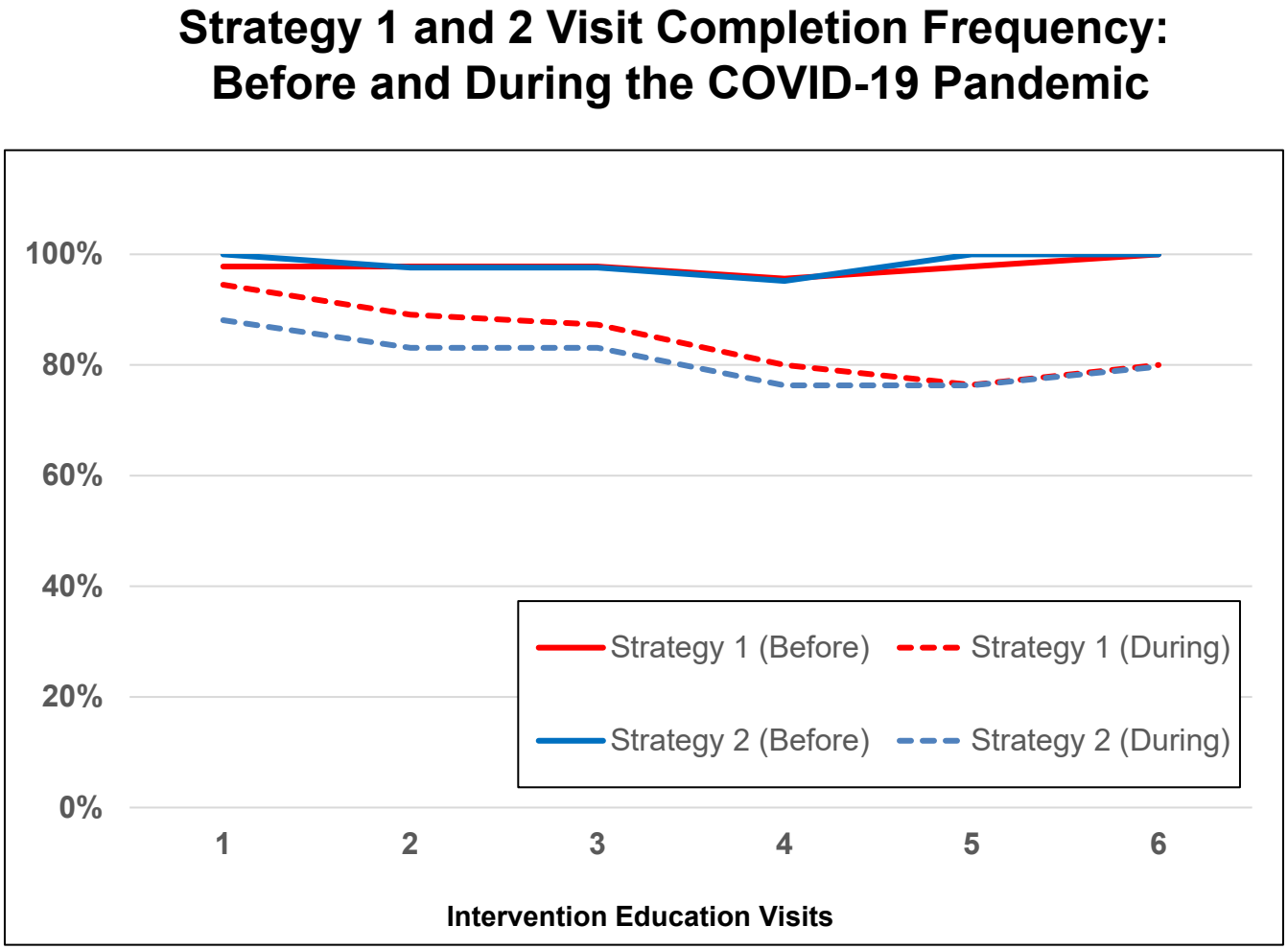
SuperWIN Trial Profile



Baseline Characteristics

Variable	Control (n=46)	Strategy 1 (n=100)	Strategy 2 (n=101)
Age - mean- yr	56.2 (11.4)	57.0 (10.7)	55.8 (11.0)
Female- N (%)	32 (69.6%)	68 (68.0%)	71 (70.3%)
Race- N (%)			
Black or African American	6 (13.0%)	23 (23.0%)	22 (21.8%)
White	36 (78.3%)	73 (73.0%)	72 (71.3%)
Married/Living with Partner- N (%)	30 (65.2%)	70 (70.0%)	60 (59.4%)
Employed full-time (40 or more hours per week)- N (%)	25 (54.3%)	60 (60.0%)	47 (46.5%)
Graduate degree - N (%)	14 (30.4%)	27 (27.0%)	32 (31.7%)
Annual household income $125,000 or more – N (%)	13 (28.3%)	37 (37.0%)	40 (39.6%)
Children living in the household – mean (SD)	0.33 (0.67)	0.43 (0.89)	0.42 (0.89)
Major challenge in sticking to a diet (top 3 reasons)- N (%)			
Busy schedule/Not enough time	6 (13.0%)	32 (32.0%)	18 (17.8%)
Diet too repetitive or strict	10 (21.7%)	16 (16.0%)	29 (28.7%)
Lack of cooking or meal planning skills	11 (23.9%)	18 (18.0%)	25 (24.8%)
Prior myocardial infarction or stroke - N (%)	5 (10.9%)	7 (7.0%)	5 (5.0%)
Treated with hypertension meds - N (%)	31 (67.4%)	77 (77.0%)	73 (72.3%)
Blood pressure- mean (SD) - mm Hg			
Systolic	130.0 (16.4)	129.8 (18.6)	128.4 (14.9)
Diastolic	85.7 (11.1)	82.1 (11.6)	83.4 (10.4)
Body mass index- mean (SD) - kg/m^2	33.8 (7.2)	34.0 (7.9)	32.9 (8.1)
Treatment with hypercholesterolemia medications - N (%)	20 (43.5%)	47 (47.0%)	37 (36.6%)
Non-HDL cholesterol – mean (SD)- mg/dl	107.0 (32.5)	115.2 (37.0)	112.5 (35.3)
Triglycerides[b]- mean (SD)- mg/dl	170.5 (84.1)	173.0 (95.3)	159.2 (96.2)

Impact of COVID-19 on SuperWIN



Results at 3 months

First Hypothesis:

Does a 6-Session Educational Intervention, Guided by Purchasing Data, Conducted in the Store by a RD Increase DASH Score (adherence)?

Overall Cohort	Control (N=46)	Strategy 1 (N=100)	Strategy 2 (N=101)	Strategies 1 and 2 vs. Control	P-value
At baseline	45.2 (42.0, 48.4)	44.4 (42.0, 46.8)	43.2 (40.8, 45.5)		
At 3 months	51.0 (47.6, 54.4)	53.1 (50.6, 55.5)	55.6 (53.2, 58.1)		
DASH Change	***5.8 (2.5, 9.2)***	***8.6 (6.4, 10.8)***	***12.4 (10.3, 14.6)***	***4.7 (0.9, 8.5)***	***0.02***
Data are reported as least-squares means (95%CI).					

Results at 3 months

First Hypothesis:

Does a 6-Session Educational Intervention, Guided by Purchasing Data, Conducted in the Store by a RD Increase DASH Score (adherence)?

Overall Cohort	Control (N=46)	Strategy 1 (N=100)	Strategy 2 (N=101)	Strategies 1 and 2 vs. Control	P-value
At baseline	45.2 (42.0, 48.4)	44.4 (42.0, 46.8)	43.2 (40.8, 45.5)		
At 3 months	51.0 (47.6, 54.4)	53.1 (50.6, 55.5)	55.6 (53.2, 58.1)		
DASH Change	***5.8 (2.5, 9.2)***	***8.6 (6.4, 10.8)***	***12.4 (10.3, 14.6)***	***4.7 (0.9, 8.5)***	***0.02***
Data are reported as least-squares mean (95%CI).					

Pre-COVID Subgroup*	(N=22)	(N=45)	(N=42)		
At baseline	45.1 (39.9, 50.4)	42.6 (38.6, 46.6)	42.7 (38.4, 47.0)		
At 3 months	48.9 (43.6, 54.2)	53.2 (49.2, 57.2)	56.4 (52.1, 60.7)		
DASH Change	***3.8 (-0.7, 8.2)***	***10.6 (7.5, 13.7)***	***13.7 (10.5, 16.9)***	***8.3 (3.4, 13.3)***	***0.001***

*Prespecified prior to database lock

Results at 3 months

<u>Second Hypothesis:</u>
Does the addition of online shopping and other technologies increase DASH Score (adherence)?

Overall Cohort	Control (N=46)	Strategy 1 (N=100)	Strategy 2 (N=101)	Strategy 2 vs. 1	P-value
At baseline	45.2 (42.0, 48.4)	44.4 (42.0, 46.8)	43.2 (40.8, 45.5)		
At 3 months	51.0 (47.6, 54.4)	53.1 (50.6, 55.5)	55.6 (53.2, 58.1)		
DASH Change	***5.8 (2.5, 9.2)***	***8.6 (6.4, 10.8)***	***12.4 (10.3, 14.6)***	***3.8 (0.8, 6.9)***	***0.01***
Data are reported as least-squares mean (95%CI).					

Results at 3 months

<u>Second Hypothesis:</u>
Does the addition of online shopping and other technologies increase DASH Score (adherence)?

Overall Cohort	Control (N=46)	Strategy 1 (N=100)	Strategy 2 (N=101)	Strategy 2 vs. 1	P-value
At baseline	45.2 (42.0, 48.4)	44.4 (42.0, 46.8)	43.2 (40.8, 45.5)		
At 3 months	51.0 (47.6, 54.4)	53.1 (50.6, 55.5)	55.6 (53.2, 58.1)		
DASH Change	**5.8 (2.5, 9.2)**	**8.6 (6.4, 10.8)**	**12.4 (10.3, 14.6)**	***3.8 (0.8, 6.9)***	***0.01***
Data are reported as least-squares mean (95%CI).					

Pre-COVID Subgroup	(N=22)	(N=45)	(N=42)		
At baseline	45.1 (39.9, 50.4)	42.6 (38.6, 46.6)	42.7 (38.4, 47.0)		
At 3 months	48.9 (43.6, 54.2)	53.2 (49.2, 57.2)	56.4 (52.1, 60.7)		
DASH Change	***3.8 (-0.7, 8.2)***	***10.6 (7.5, 13.7)***	***13.7 (10.5, 16.9)***	***3.1 (-1.3, 7.6)***	***0.17***

Secondary Results: DASH at 6 months

Does increased DASH adherence persist at 6 months?

Overall Cohort	Control (n=46)	Strategy 1 (n=100)	Strategy 2 (n=101)	Strategies 1 and 2 vs. Control	P-value	Strategy 2 vs. 1	P-value
At baseline	45.2 (42.0, 48.4)	44.4 (42.0, 46.8)	43.2 (40.8, 45.5)				
At 6 months	49.6 (46.3, 52.8)	51.0 (48.6, 53.5)	51.6 (49.2, 54.0)				
DASH Change	***4.4 (0.6, 8.1)***	***6.6 (4.0, 9.2)***	***8.4 (5.9, 11.0)***	***3.1 (-1.0, 7.3)***	***0.14***	***1.8 (-1.9, 5.5)***	***0.34***
Data are reported as least-squares mean (95%CI).							

Secondary Results: DASH at 6 months

Does increased DASH adherence persist at 6 months?

Overall Cohort	Control (n=46)	Strategy 1 (n=100)	Strategy 2 (n=101)	Strategies 1 and 2 vs. Control	P-value	Strategy 2 vs. 1	P-value
At baseline	45.2 (42.0, 48.4)	44.4 (42.0, 46.8)	43.2 (40.8, 45.5)				
At 6 months	49.6 (46.3, 52.8)	51.0 (48.6, 53.5)	51.6 (49.2, 54.0)				
DASH Change	***4.4 (0.6, 8.1)***	***6.6 (4.0, 9.2)***	***8.4 (5.9, 11.0)***	***3.1 (-1.0, 7.3)***	***0.14***	***1.8 (-1.9, 5.5)***	***0.34***
Data are reported as least-squares mean (95%CI).							

Pre-COVID Subgroup	(N=22)	(N=45)	(N=42)				
At baseline	45.1 (39.9, 50.4)	42.6 (38.6, 46.6)	42.7 (38.4, 47.0)				
At 6 months	49.8 (44.5, 55.1)	51.9 (47.8, 55.9)	53.1 (48.8, 57.5)				
DASH Change	**4.7 (-0.6, 10.0)**	**9.3 (5.5, 13.0)**	**10.4 (6.6, 14.3)**	***5.1 (-0.8, 11.1)***	***0.09***	***1.2 (-4.2, 6.6)***	***0.67***

Secondary Results: Biometrics at 3 months

Did changes in dietary impact improve other health measures?

	Control (n=46)	Strategy 1 (n=100)	Strategy 2 (n=101)	Strategies 1 and 2 vs. Control	P-value	Strategy 2 vs. 1	P-value
Systolic BP – mmHg							
At baseline	125.9 (119.1, 132.7)	125.6 (119.7, 131.5)	125.0 (119.0, 130.9)				
At 3 months	123.2 (116.2, 130.1)	118.9 (113.0, 124.9)	119.2 (113.3, 125.2)				
Change	***-2.8 (-7.1, 1.6)***	***-6.6 (-9.8, -3.4)***	***-5.7 (-8.7, -2.8)***	***-3.4 (-8.4, 1.6)***	***0.18***	***0.9 (-3.2, 5.0)***	***0.66***
Diastolic BP – mmHg							
At baseline	82.8 (78.2, 87.5)	79.2 (75.1, 83.2)	81.4 (77.3, 85.6)				
At 3 months	80.2 (75.5, 84.9)	76.7 (72.6, 80.9)	79.4 (75.1, 83.7)				
Change	***-2.6 (-5.5, 0.2)***	***-2.4 (-4.2, -0.6)***	***-2.0 (-3.9, -0.1)***	***0.4 (-2.7, 3.6)***	***0.79***	***0.4 (-2.1, 2.9)***	***0.76***
BMI - kg/m^2							
At baseline	37.9 (34.2, 41.7)	38.1 (34.8, 41.4)	37.1 (33.7, 40.5)				
At 3 months	37.7 (33.9, 41.4)	37.7 (34.3, 41.0)	36.3 (32.9, 39.8)				
Change	***-0.2 (-0.6, 0.1)***	***-0.4 (-0.7, -0.2)***	***-0.8 (-1.0, -0.5)***	***-0.4 (-0.8, 0.0)***	***0.08***	***-0.3 (-0.7, 0.0)***	***0.06***

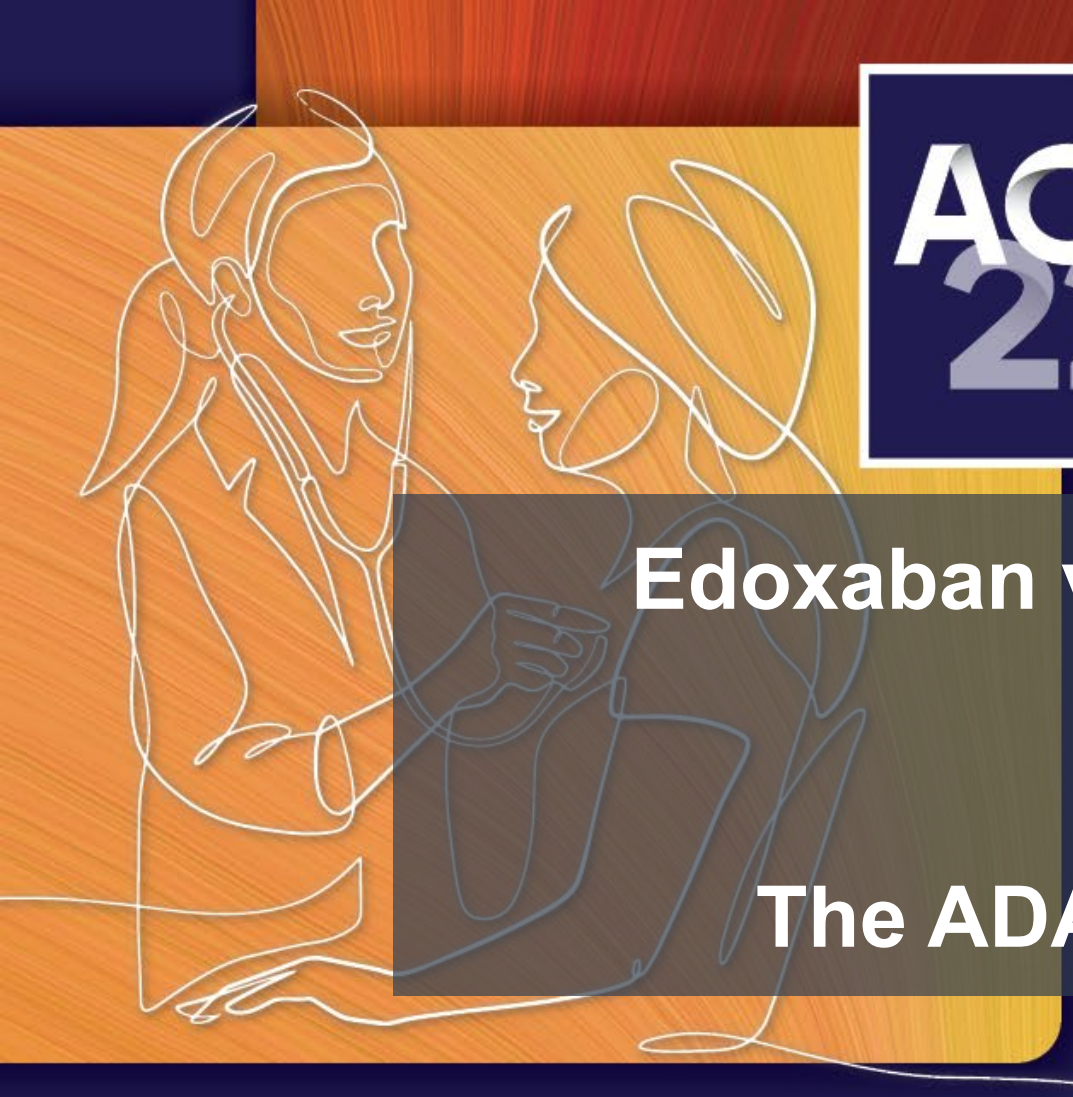
Data are reported as least-squares mean (95%CI).

Summary

- SuperWIN demonstrated the efficacy of dietary interventions harnessing the store's physical environment, RDs, and purchasing data.
- SuperWIN demonstrated the efficacy of the online shopping tools and applications being rapidly adopted by the public.
- Pre-COVID metrics demonstrated near-perfect visit attendance suggesting the participants' experiences were optimized by using the stores at which they routinely shopped.

And finally…

- SuperWIN was made possible by a unique-to-date research collaboration between a diverse academic team and a large retailer.
- A new era of research collaborations between academia and retailers is needed to extend the reach of healthcare beyond traditional systems and to address many of the most pressing public health challenges.



Edoxaban versus Dual Antiplatelet Therapy for Leaflet Thrombosis and Cerebral Thromboembolism after TAVR: The ADAPT-TAVR Randomized Clinical Trial

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

Duk-Woo Park, MD, PhD

For the ADAPT-TAVR Investigators,

Asan Medical Center,

University of Ulsan College of Medicine, Seoul, Korea

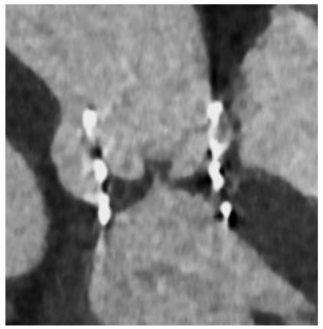
Twitter (@dukwoo_park)

Disclosure

- The ADAPT-TAVR trial was an investigator-initiated trial and was funded by the CardioVascular Research Foundation (Seoul, Korea) and Daiichi Sankyo Korea Co., Ltd.
- The funders assisted in the design of the protocol but had no role in the conduct of the trial or in the analysis, interpretation, or reporting of the results.

Subclinical Leaflet Thrombosis (SLT) after TAVR[1-4]

What is Known? and What is Unknown?



>75% of leaflet

SLT

Unknown

Causal association of SLT and cerebral embolism

Cerebral thromboembolism
Stroke or TIA

Known

OAC can reduce SLT

OAC therapy

Unknown

OAC can reduce SLT-related cerebral embolism

SLT, subclinical leaflet thrombosis; OAC, oral anticoagulation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

[1]Makkar RR, et al. *NEJM*. 2015;373:2015-2024. [2]Chakravarty T, et al. *Lancet* 2017;389:2383-2392. [3]Makkar RR, et al. *JACC* 2020;75:3003-3015. [4]Bogyi M, et al. *JACC: Cardiovascular Interventions* 2021;14:2643-2656.

Background

- The incidence of subclinical leaflet thrombosis by 4D-CT was not uncommon (approximately 10%~30%) and this phenomenon could be associated with increased risks of cerebral thromboembolism, stroke or TIA.[1-4]
- However, the causal relationship of leaflet thrombosis with cerebral thromboembolism and neurological/neurocognitive dysfunction in patients undergoing TAVR is still unclear.
- Several RCTs have tested that NOAC-based strategy is more effective than conventional antithrombotic strategies for the prevention of leaflet thrombosis and thromboembolic risk in patients with or without OAC indication after TAVR.[5-8]

4D-CT, four-dimensional computed tomography; NOAC, non-vitamin K direct anticoagulant; OAC, oral anticoagulation; RCTs, randomized controlled trials; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

[1]Chakravarty T, et al. *Lancet* 2017;389:2383-2392. [2]Rashid HN, et al. *EuroIntervention* 2018;13:e1748-e1755. [3]Makkar RR, et al. *JACC* 2020;75:3003-3015. [4]Bogyi M, et al. *JACC: Cardiovascular Interventions* 2021;14:2643-2656. [5]Dangas GD et al. *NEJM* 2020;382:120-129. [6]Collet JP. et al. *ATLANTIS trial*. *ACC* 2021. [7]De Backer O et al. *NEJM* 2020;382:130-139. [8]Van Mieghem NM et al. *NEJM* 2021; 385:2150-2160.

Study Objectives

- Primary objective → to investigate the effect of edoxaban compared to DAPT for the prevention of leaflet thrombosis and the accompanying potential risks of cerebral thromboembolization and neurological or neurocognitive dysfunction in patients without an OAC indication after TAVR.

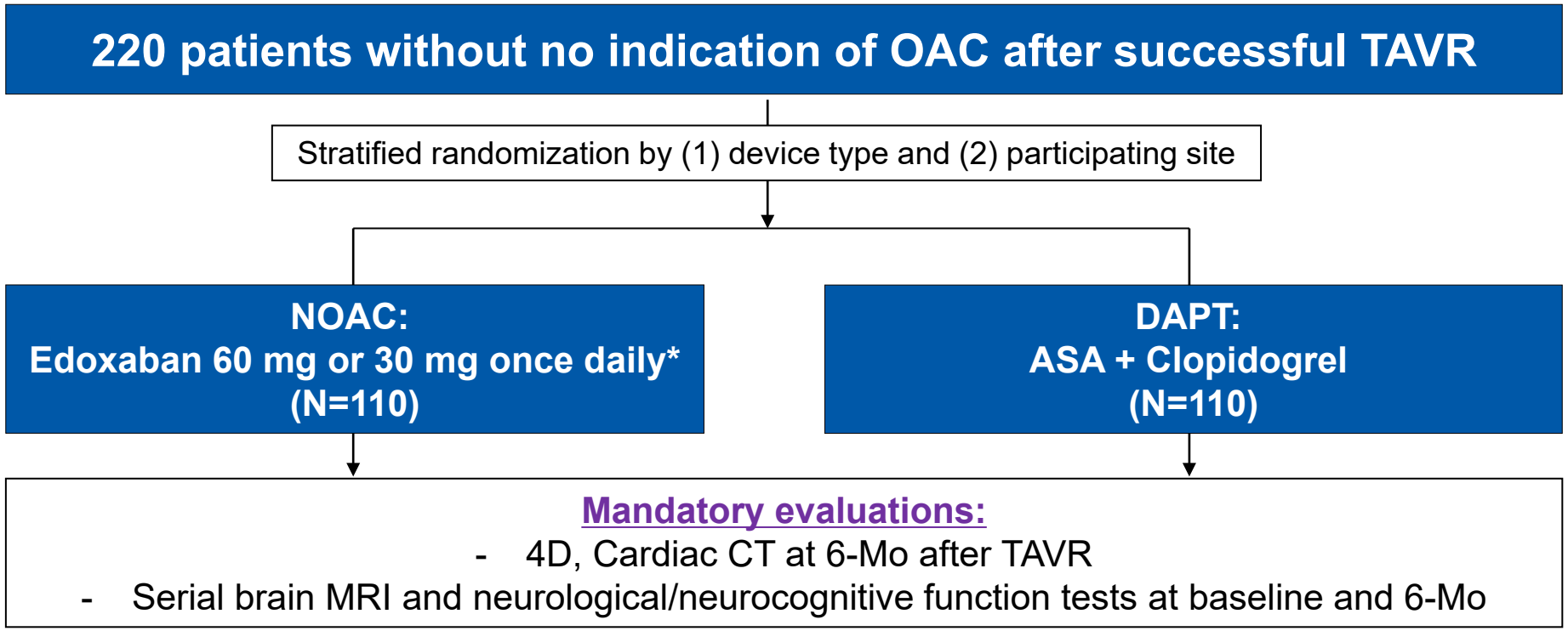
- Secondary objective → to determine the causal relationship of subclinical leaflet thrombosis with cerebral thromboembolism and neurological/neurocognitive dysfunction.

DAPT, dual antiplatelet therapy; OAC, oral anticoagulation; TAVR, transcatheter aortic valve replacement

Study Design

ADAPT-TAVR Trial:

Anticoagulant versus ***D***ual ***A***ntiplatelet Therapy for ***P***reventing Leaflet ***T***hrombosis After ***T***ranscatheter ***A***ortic ***V***alve ***R***eplacement



*30 mg once daily if moderate or severe renal impairment (creatinine clearance 15 – 50 mL/min), low body weight ≤60kg, or concomitant use of P-glycoprotein inhibitors (cyclosporin, dronedarone, erythromycin, ketoconazole).

Park H et al. BMJ Open. 2021;11:e042587

Inclusion and Exclusion Criteria

INCLUSION

1. Man or woman (≥ 18 years) **with symptomatic AS**

2. Have a **successful TAVR** of an aortic valve stenosis (either native of valve-in-valve), defined as:
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location.[1]
   - Intended performance of the prosthetic heart valve - presence of all 3 conditions post-TAVR:
     - Mean aortic valve gradient < 20 mmHg
     - Peak transvalvular velocity (aortic valve maximum velocity) < 3.0 m/s
     - No severe or moderate aortic valve regurgitation
   - Without unresolved periprocedural complications

3. With **any approved/marketed TAVR device**

KEY EXCLUSION

1. Any established indication for anticoagulation (e.g., atrial fibrillation)
2. Any absolute indication for DAPT (e.g., ACS or recent PCI)
3. Severe renal insufficiency prohibiting CT imaging (eGFR<30)
4. Contraindication to aspirin, clopidogrel or edoxaban
5. Known bleeding diathesis
6. Clinically overt stroke within 3 months
7. Moderate and severe hepatic impairment or any hepatic disease associated with coagulopathy
8. Active malignancy

[1]Kappetein AP, et al. *J Am Coll Cardiol*. 2012;60:1438-1454.

Study Endpoints

Primary endpoint

- Incidence of leaflet thrombosis on 4D, volume-rendered CT at 6 months

Secondary endpoints

- Presence and number/volume of new cerebral lesions on brain MRI
- Serial change of neurological/neurocognitive assessment (NIHSS, mRS, and MoCA)
- Clinical safety and efficacy outcomes
- Serial echocardiographic parameters

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment

Enrollment: 5 centers, 3 countries

Asan Medical Center
- DW Park, SJ Park
CHA Bundang Medical Center
- WJ Kim, SH Kang

Queen Mary Hospital
- SCC Lam, AYT Wong

Cheng Hsin General Hospital
- WH Yin, J Wei, YT Lee
National Taiwan University Hospital
- HL Kao, MS Lin, TY Ko

Executive Committee: DW Park (Trial PI), SJ Park, SCC Lam, WH Yin, HL Kao, WJ Kim
Data Monitoring Committee: MS Lee (Chairperson), BK Koo, YG Ko, YH Jeong, JH Kim
Clinical Events Committee: CH Lee (Chairperson), JH Lee, JH Kim

Imaging (CT and MRI) Core Lab: Asan Image Metrics (Imaging Corelab), KW Kim (Chairperson), DH Yang (CT corelab), SC Jung (MRI corelab)

Neurocognitive function and echo Core Lab: JH Lee (Chair, Neurology Corelab), SA Lee (Chair, Echo. Corelab)

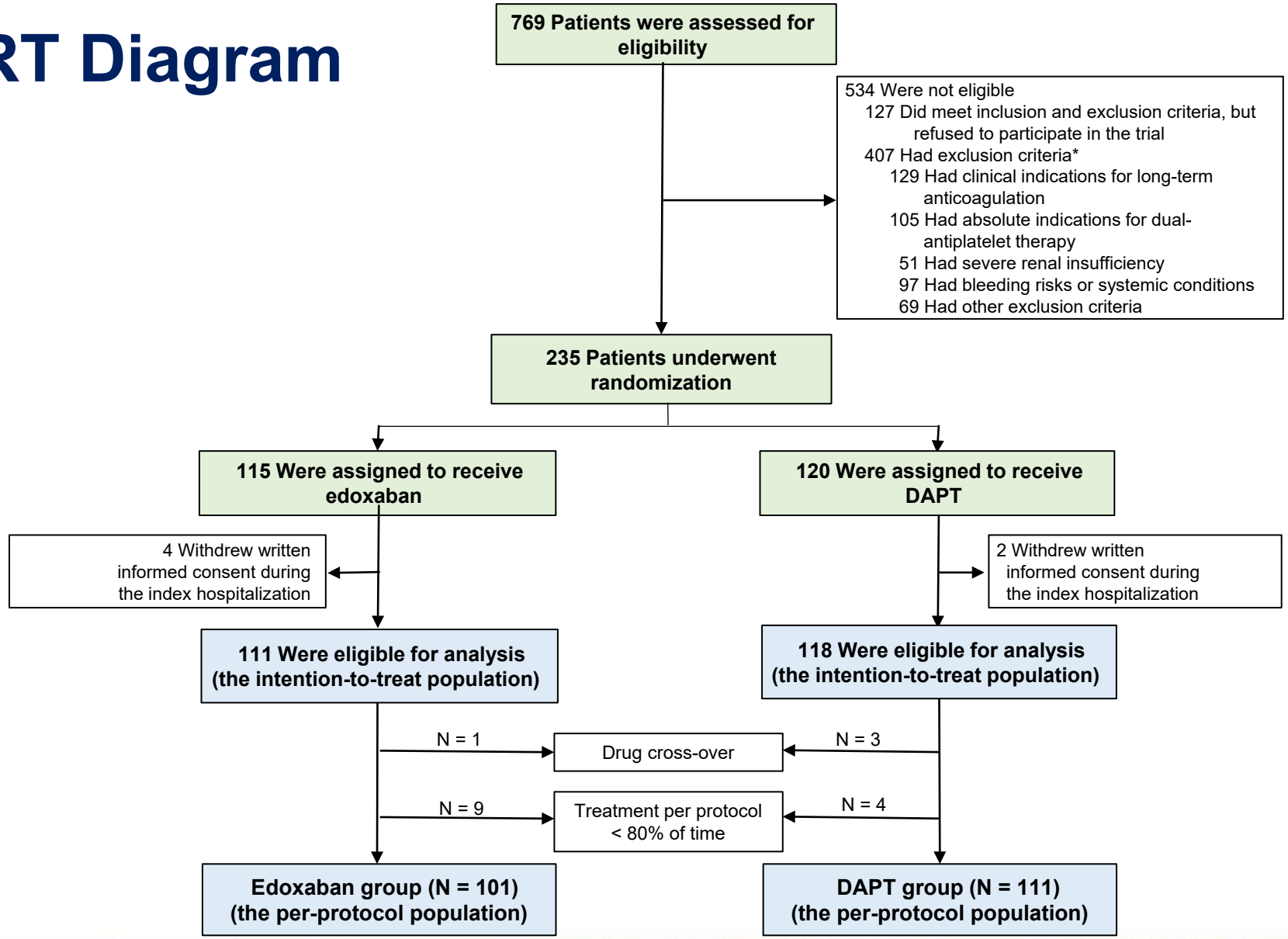
Sample Size & Statistical Analysis

- Under an assumption that an incidence of leaflet thrombosis of 15% in the DAPT group and 3% in the NOAC (edoxaban) group based on prior data,[1] a total sample of 220 patients was deemed to be sufficient to evaluate the primary endpoint with a statistical power of 80%, a 2-sided significance level of 0.05 and attrition rate of 10% (CT follow-up loss).
- The final sample size was also met to demonstrate that the edoxaban group would provide a 30% reduction of the number of new cerebral lesions on MRI compared to the DAPT group based on prior available data[2-3]
- The main analyses were performed according to the ITT principle and secondary analyses were also performed in the PP population

ITT, intention-to-treat; PP, per-protocol.

[1]Chakravarty T, et al. *Lancet* 2017;389:2383-2392. [2]Haussig S, et al. *JAMA* 2016;316:592-601. [3]Kapadia SR, et al. *JACC* 2017;69:367-377 .

CONSORT Diagram



Baseline Characteristics, ITT Population

	Edoxaban group (N=111)	DAPT group (N=118)
Clinical characteristics		
Age, years	80.2±5.2	80.0±5.3
Male sex	49 (44.1%)	47 (39.8%)
Body weight ≤60kg	55 (49.6%)	63 (53.4%)
STS risk score	3.1±2.1	3.5±2.7
EuroSCORE II value	2.3±3.5	2.4±2.1
NYHA class III or IV	30 (27.0%)	31 (26.3%)
Diabetes mellitus	35 (31.5%)	36 (30.5%)
Coronary artery disease	32 (28.8%)	34 (28.8%)
Prior PCI	18 (16.2%)	14 (11.9%)
Prior cerebrovascular dis.	6 (5.4%)	11 (9.3%)
Peripheral artery disease	7 (6.3%)	11 (9.3%)
Chronic lung disease	25 (22.5%)	31 (26.3%)
Creatine clearance (ml/min)	61.0±21.5	59.2±18.7
Creatine clearance ≤50	38 (34.2)	47 (39.8)
Use of low-dose edoxaban	68 (61.3%)	-

	Edoxaban group (N=111)	DAPT group (N=118)
Procedural characteristics		
Pre-TAVR balloon angioplasty	40 (36.0%)	41 (34.8%)
Valve type		
Balloon-expandable	101 (91.0%)	105 (89.0%)
Self-expandable	10 (9.0%)	13 (11.0%)
Valve-in-valve	0 (0.0)	4 (3.4%)
Transfemoral approach	110 (99.1%)	117 (99.2%)
MAC anesthesia	84 (75.7%)	92 (78.0%)
New permanent pacemaker	13 (11.7%)	13 (11.0%)
Post-TAVR echo characteristics		
AV area, cm^2	1.7±0.4	1.6±0.4
Mean AV gradient, mmHg	13.4±5.1	14.3±5.4
LVEF, %	64.4±10.0	64.2±9.5
Paravalvular aortic regurgitation		
Mild	105 (97.2%)	112 (97.3%)
Moderate or severe	3 (2.8%)	3 (2.7%)

AV, aortic valve; LVEF, left ventricular ejection fraction; MAC, Monitored anesthetic care; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

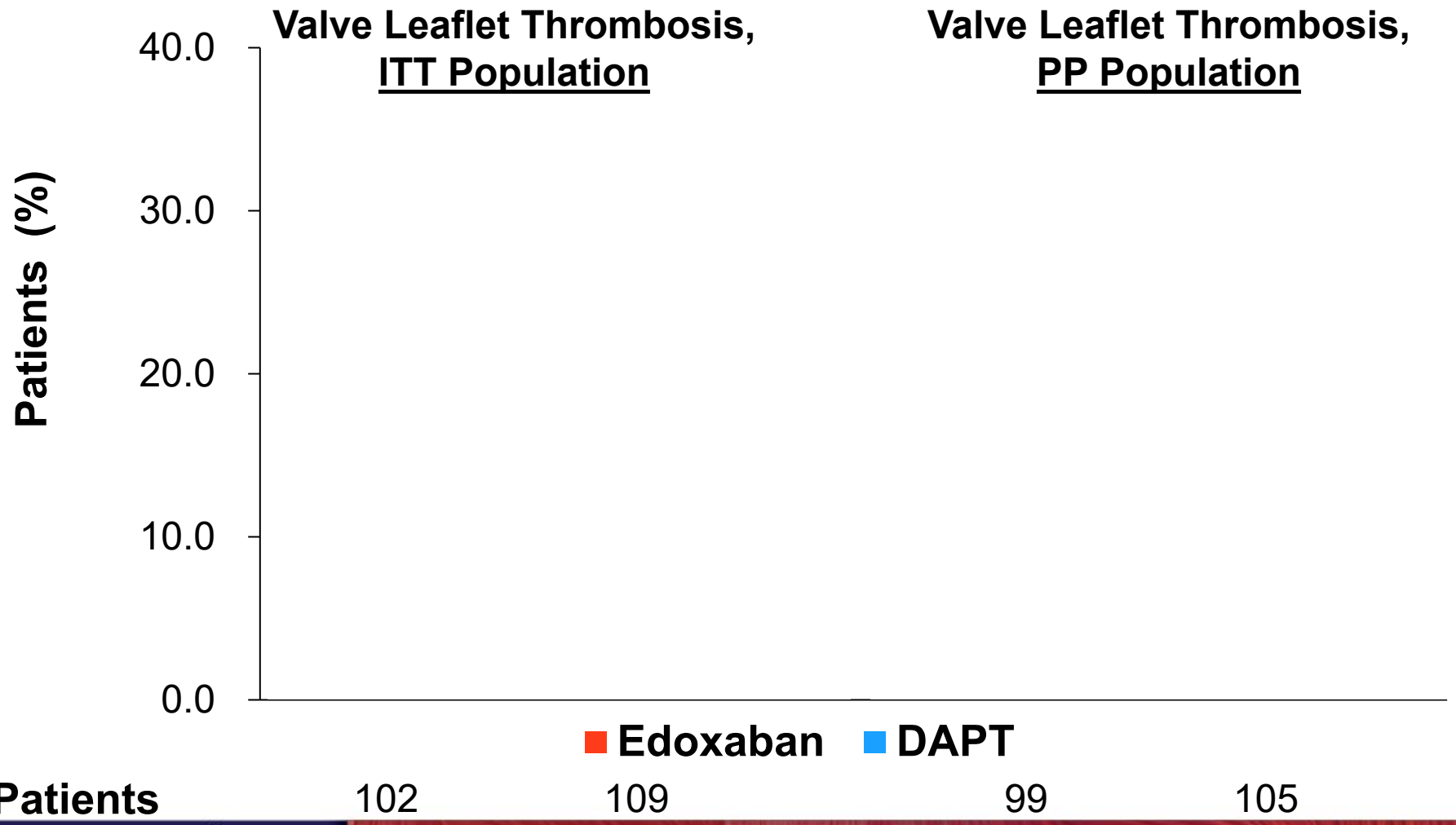
Completeness of Imaging & Neurocognitive Assessment

Measurement	Cardiac CT	Brain MRI	NIHSS	mRS	MoCA
Post-TAVR (~ before Discharge)		★ (98.3%)	★ (98.3%)	★ (98.3%)	★ (98.3%)
6-Mo follow-up	★ (95.9%)	★ (96.4%)	★ (95.5%)	★ (95.5%)	★ (95.5%)
Completeness of serial matching*		95.9%	93.7%	93.7%	93.7%

* Completeness of imaging or neurological assessments at 6 months was estimated among eligible patients who were alive at 6 months and did not withdraw during follow-up.

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment

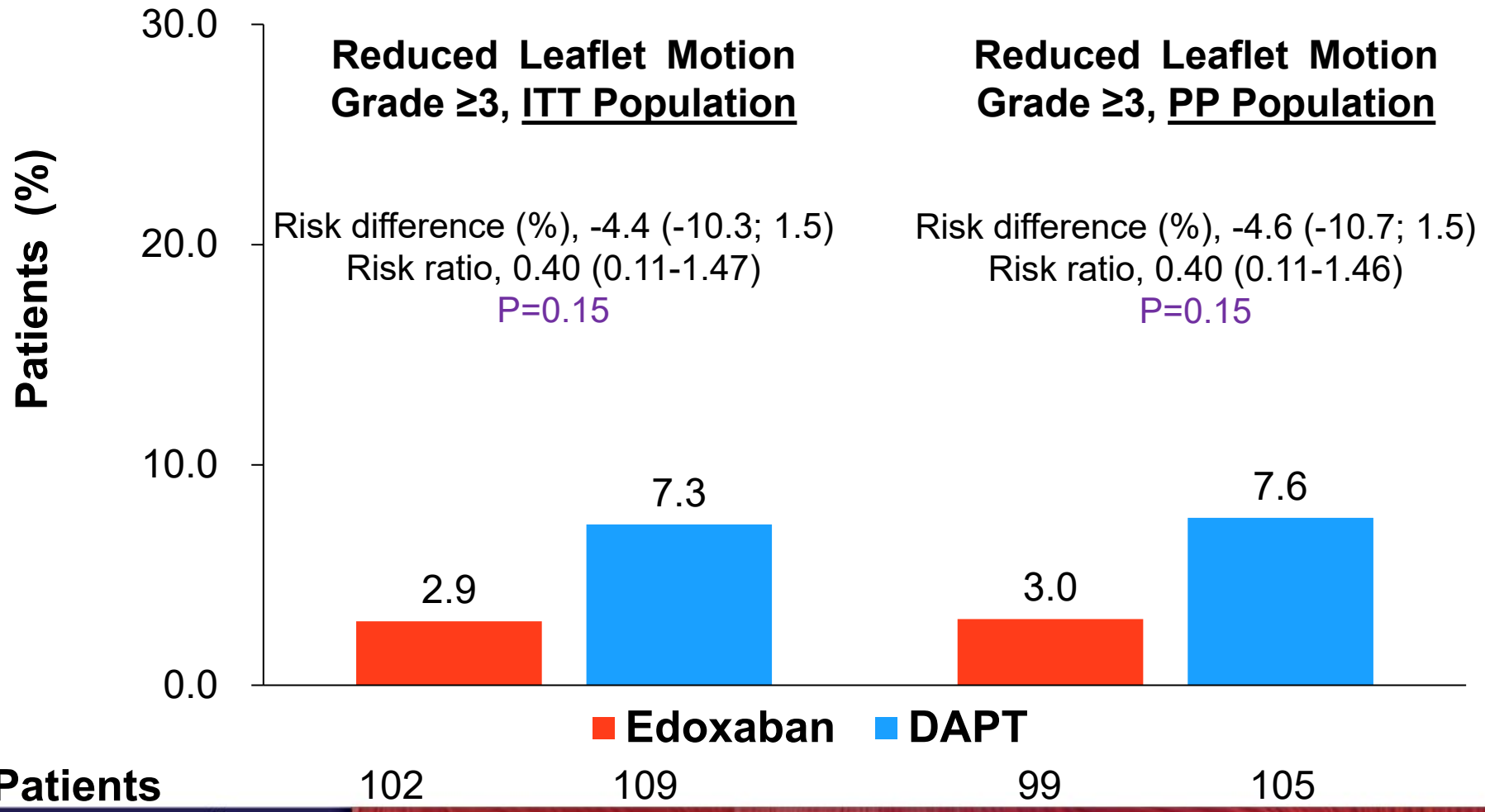
4D-CT Primary End Points



The degree of hypoattenuated leaflet thickening and the severity of reduced leaflet motion were classified according to the standard definition (Blanke P, et al. JACC Cardiovasc Imaging. 2019;12:1-24)

*P values are derived from the chi-square test or Fisher's exact test as appropriate.

4D-CT Outcomes

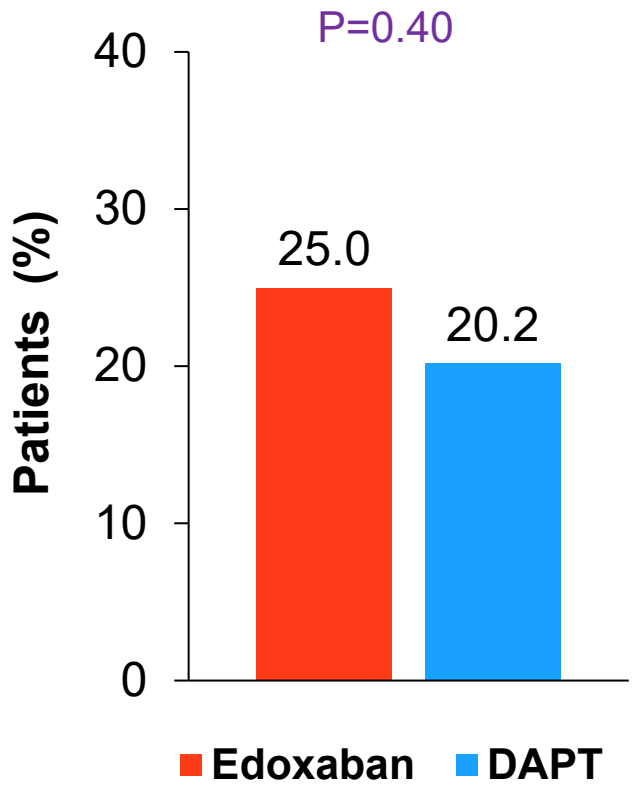


The degree of hypoattenuated leaflet thickening and the severity of reduced leaflet motion were classified according to the standard definition (Blanke P, et al. JACC Cardiovasc Imaging. 2019;12:1-24)

*P values are derived from the chi-square test or Fisher's exact test as appropriate.

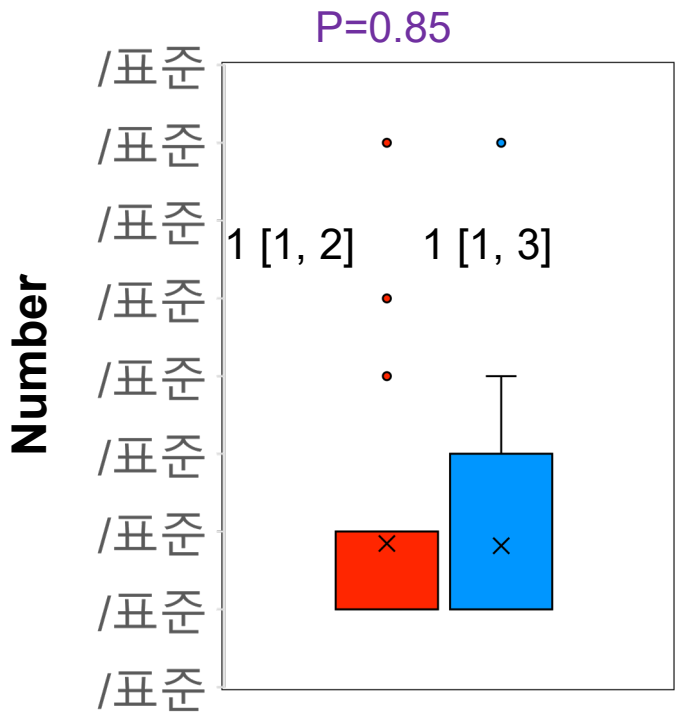
MRI End Points, ITT Analysis

Presence of New Cerebral Lesions



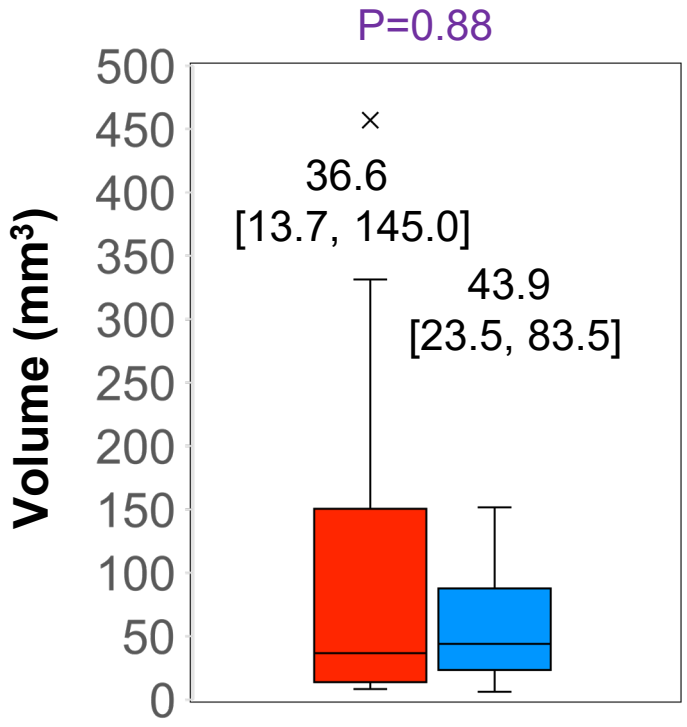
No. of Patients	104	109

Median Number of Total New Lesions



104	109

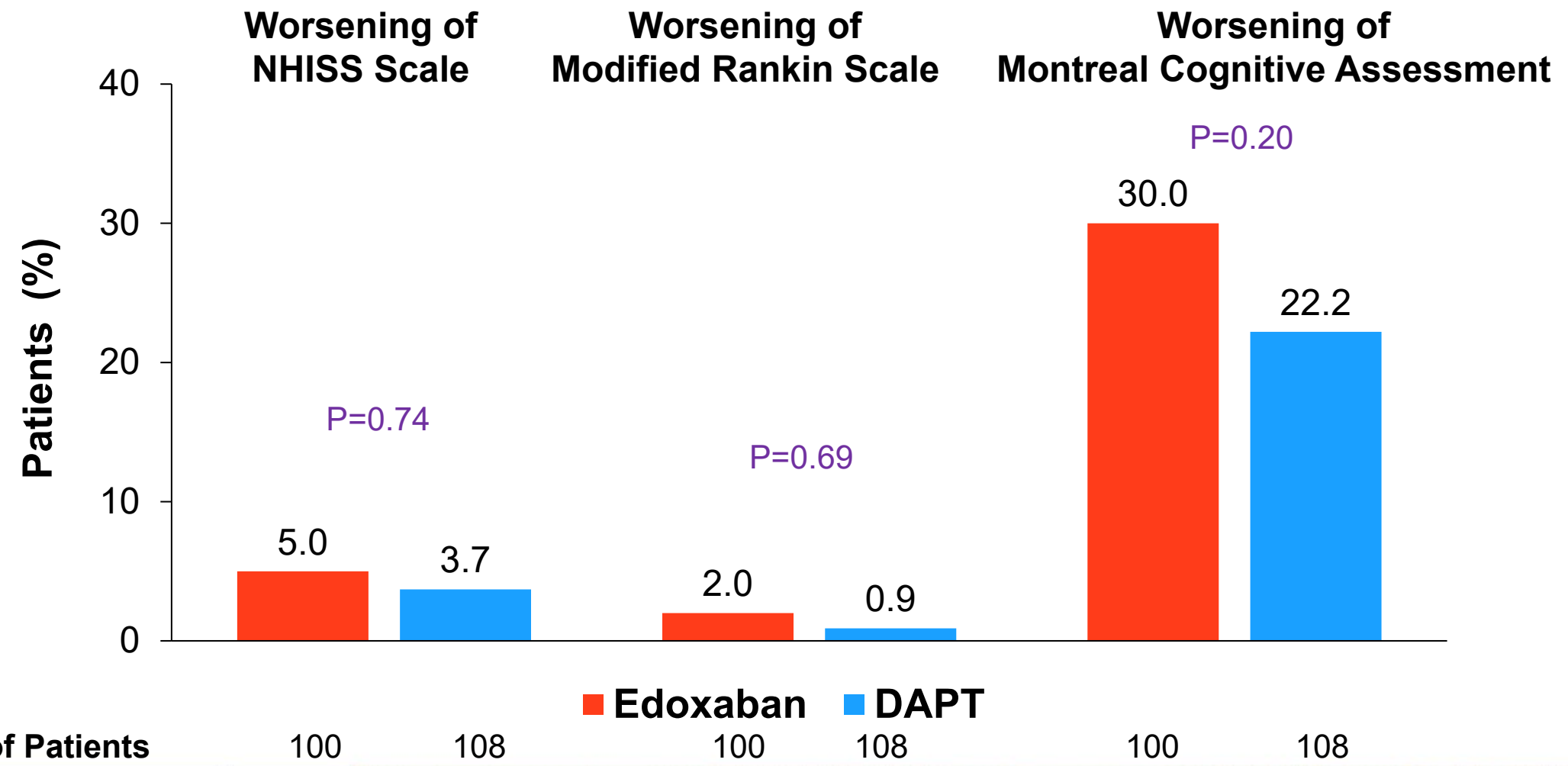
Median Volume of Total New Lesions (mm^3)



104	109

P values are derived from the chi-square test or Fisher's exact test as appropriate.
Median differences calculated as independent samples Hodges-Lehmann median difference estimates.

Neurological & Neurocognitive End Points

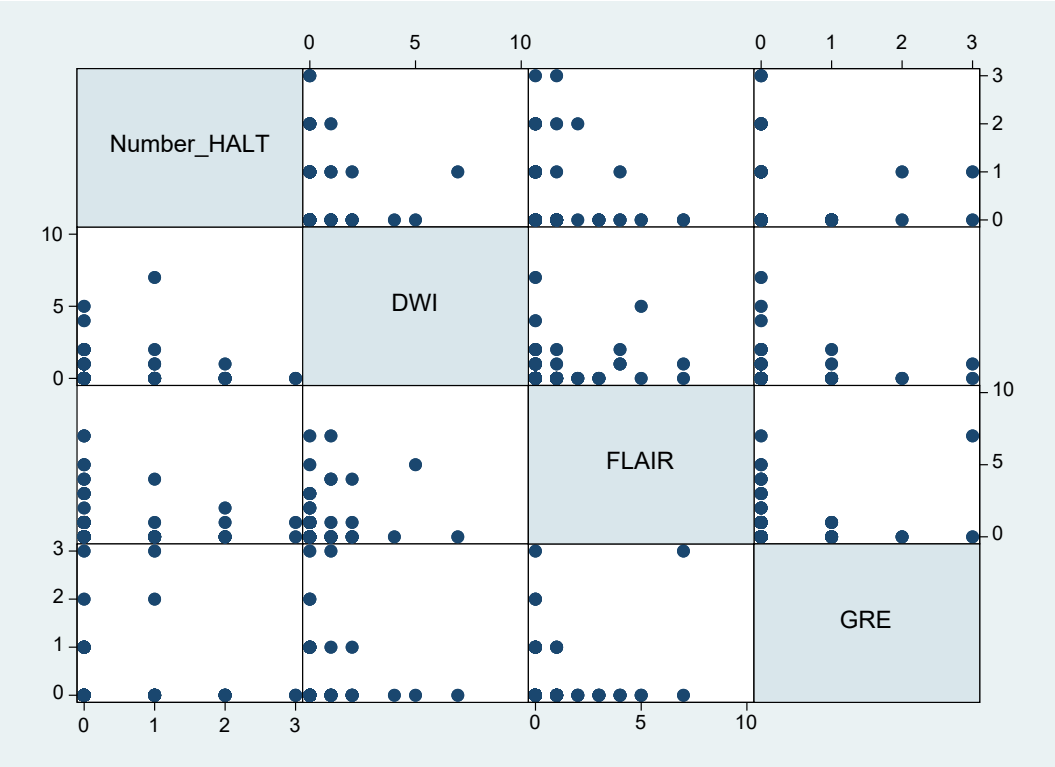


NIHSS, National Institutes of Health Stroke Scale

P values are derived from the chi-square test or Fisher's exact test as appropriate.

Worsening is defined as ≥1 point increase in NIHSS, ≥1 point increase in modified Rankin scale, or ≥1 point decrease in Montreal Cognitive Assessment scores as compared to baseline.

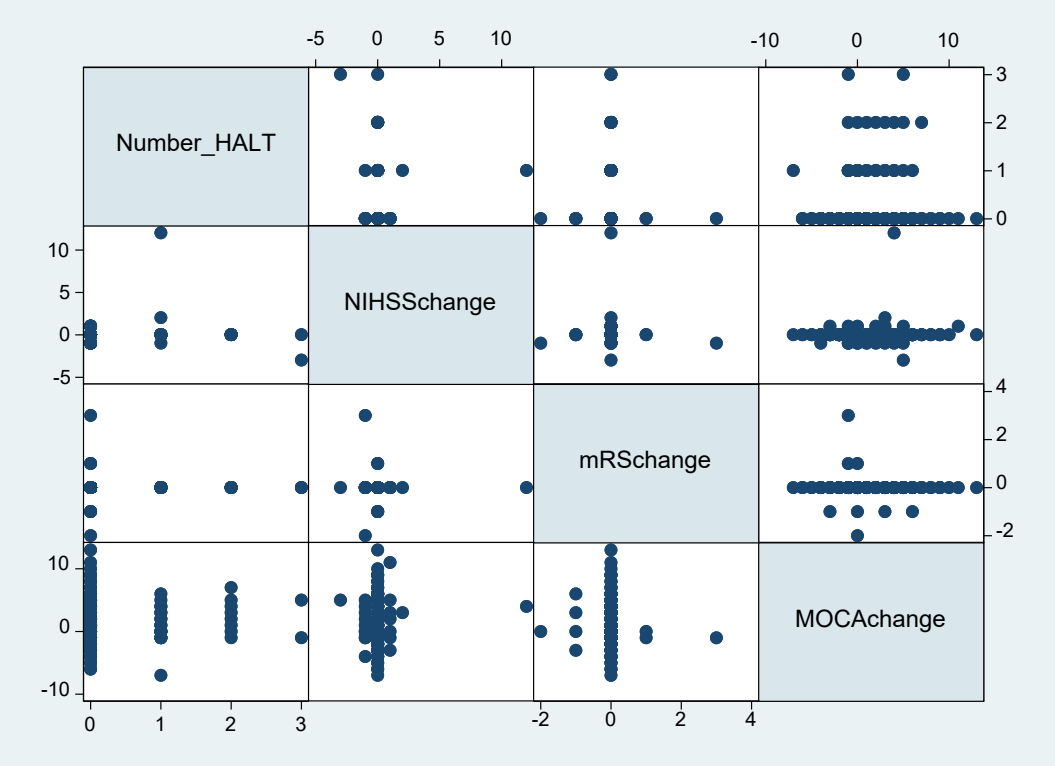
Association of Severity of HALT with Extent of New Lesions on Brain MRI



		Number of New Lesions on DWI-MRI	Number of New Lesions on FLAIR-MRI	Number of New Lesions on GRE-MRI
Number of HALT Per-Patient	N	209	209	209
	Spearman Rho	**0.09**	**-0.04**	**-0.02**
	P-Value	**0.19**	**0.60**	**0.81**

HALT, hypoattenuated leaflet thickening; DWI, diffusion weighted image; FLAIR, fluid attenuated inversion recovery; GRE, gradient echo; MRI, magnetic resonance imaging

Association of Severity of HALT with Decline of Neurological Assessments



		Serial Change of NIHSS Score	Serial Change of mRS Score	Serial Change of MOCA Score
Number of HALT Per-Patient	N	204	204	204
	Spearman Rho	**0.01**	**0.02**	**0.03**
	P-Value	**0.94**	**0.77**	**0.68**

HALT, hypoattenuated leaflet thickening; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment

Clinical Outcomes at 6 Month, ITT Population

Outcomes*	Edoxaban group (N=111) n (%)	DAPT group (N=118) n (%)	Risk Difference (95% CI)	Hazard Ratio (95% CI)†
Efficacy Outcomes				
Death	3 (2.7%)	2 (1.7%)	1.0 (-2.8; 4.8)	1.48 (0.25-8.75)
Cardiovascular death	3	0		
Non-cardiovascular death	0	2		
Stroke	2 (1.8%)	2 (1.7%)	0.1 (-3.3; 3.5)	1.05 (0.15-7.45)
Ischemic	2	2		
Hemorrhagic	0	0		
Myocardial infarction	1 (0.9%)	3 (2.5%)	-1.6 (-4.9; 1.7)	0.45 (0.05-3.83)
Systemic thromboembolic event	2 (1.8%)	0 (0)	1.8 (-0.8; 4.4)	not applicable
Safety Outcomes				
Bleeding events	13 (11.7%)	15 (12.7%)	-1.0 (-9.5; 7.5)	0.93 (0.44-1.96)
Minor bleeding	7	11		
Major bleeding	6	3		
Life-threatening or disabling bleeding	0	1		
Rehospitalization	17 (15.3%)	14 (11.9%)	3.5 (-5.4; 12.3)	1.29 (0.67-2.49)

* Clinical end points were adjudicated according to the VARC-2 and VARC-3 definitions.
† Hazard ratio (for edoxaban compared to DAPT) and corresponding 95% CI was calculated by the Cox proportional hazards models.

Limitations

- This trial was an open-label trial, which was potentially subject to reporting and ascertainment bias.
- This trial adopted surrogate imaging outcomes as the primary and key secondary end points; thus, our study was underpowered to detect any meaningful differences in clinical efficacy and safety outcomes.
- Follow-up period was relatively short; the long-term effect of leaflet thrombosis or different antithrombotic strategies on bioprosthetic valve durability is still unknown.
- Our findings cannot be directly extrapolated to patients with an established indication for OAC (approximately, one third of TAVR patients).

Conclusions

- The overall incidence of leaflet thrombosis on CT scans was less frequent (8.5% difference; risk ratio of 0.53) with the edoxaban therapy than with the DAPT therapy, although it did not reach statistical significance.

- The incidence of new cerebral thromboembolism on brain MRI and new development of neurological or neurocognitive dysfunction were not different between two groups.

- There was no association between subclinical leaflet thrombosis and temporally related changes of new cerebral thromboembolic lesions and neurological end points.

Circulation

Supplementary

Clinical Implications

- Subclinical leaflet thrombosis has not been proven to affect the clinical outcomes for patients who underwent TAVR, and thus this imaging phenomenon should not dictate the antithrombotic therapy for its prevention after TAVR.

- The absence of evidence of temporally related adverse clinical sequelae of imaging-detected subclinical leaflet thrombosis does not support the routine imaging screening tests for the detection of this phenomenon and imaging-guided antithrombotic strategies in cases without hemodynamic or clinical significance.

Cleveland Clinic

Department of OUTCOMES RESEARCH

The PROTECT Trial

Aggressive Intraoperative Warming Versus Routine Thermal Management During Noncardiac Surgery

Daniel I. Sessler, Lijian Pei, Kai Li, Shusen Cui, Matthew TV Chan, Yuguang Huang, Jingxiang Wu, Xuemei He, Gausan R. Bajracharya, Eva Rivas, Carmen KM Lam, and the PROTECT Investigators

Department of **O**UTCOMES **R**ESEARCH
(Cleveland Clinic) and 13 Chinese sites

Perioperative Hypothermia

Occurs in nearly all unwarmed surgical patients

Reported major complications (small trials, mostly old)

- Morbid cardiovascular outcomes
- Surgical site infections
- Bleeding & increased transfusion requirement

Other complications

- Decreased drug metabolism and prolonged recovery
- Thermal discomfort and shivering

Hypotheses, all tested at 30 days

Primary: aggressive warming to a core temperature near 37° C prevents a composite of myocardial injury, cardiac arrest, and death

Secondary: aggressive warming to 37° C

- Reduces deep or organ-space surgical site infections
- Decreases red cell transfusions
- Shortens hospitalization
- Decreases hospital re-admissions

Subject Selection

Inclusion

- Major elective noncardiac inpatient surgery
- General anesthesia expected to last >2 hours
- Age over 45 years
- At least one cardiac risk factor

Exclusion

- Body mass index exceeding 30 kg/m^2

Sample size: n=5,056 patients with 3 interim analyses

- 90% power for a 30% reduction in primary composite

Randomized Thermal Management

Routine thermal management: target 35.5° C

- No prewarming or fluid warming
- Forced-air cover, activated if core temp <35.5° C

Aggressive warming: target 37° C

- 30 minutes pre-warming with forced-air
- Warmed intravenous fluids
- Two intraoperative forced-air warming covers

Measurements

Intraoperative core temperature

- Esophagus or nasopharynx)

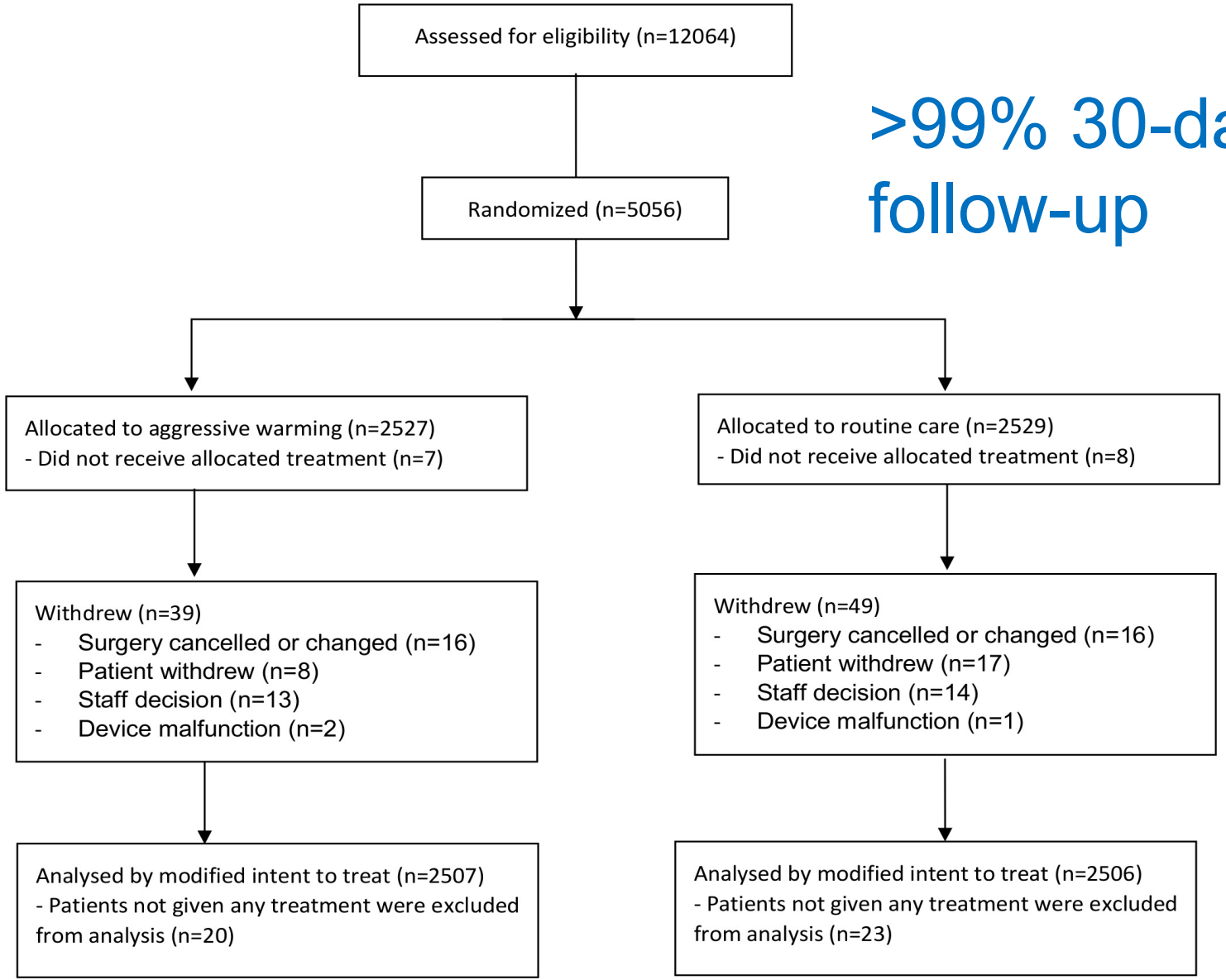
Troponin pre-operative and 1st & 2nd postop mornings

- Site-specific myocardial injury thresholds by generation and type

Deep or organ-space surgical site infections

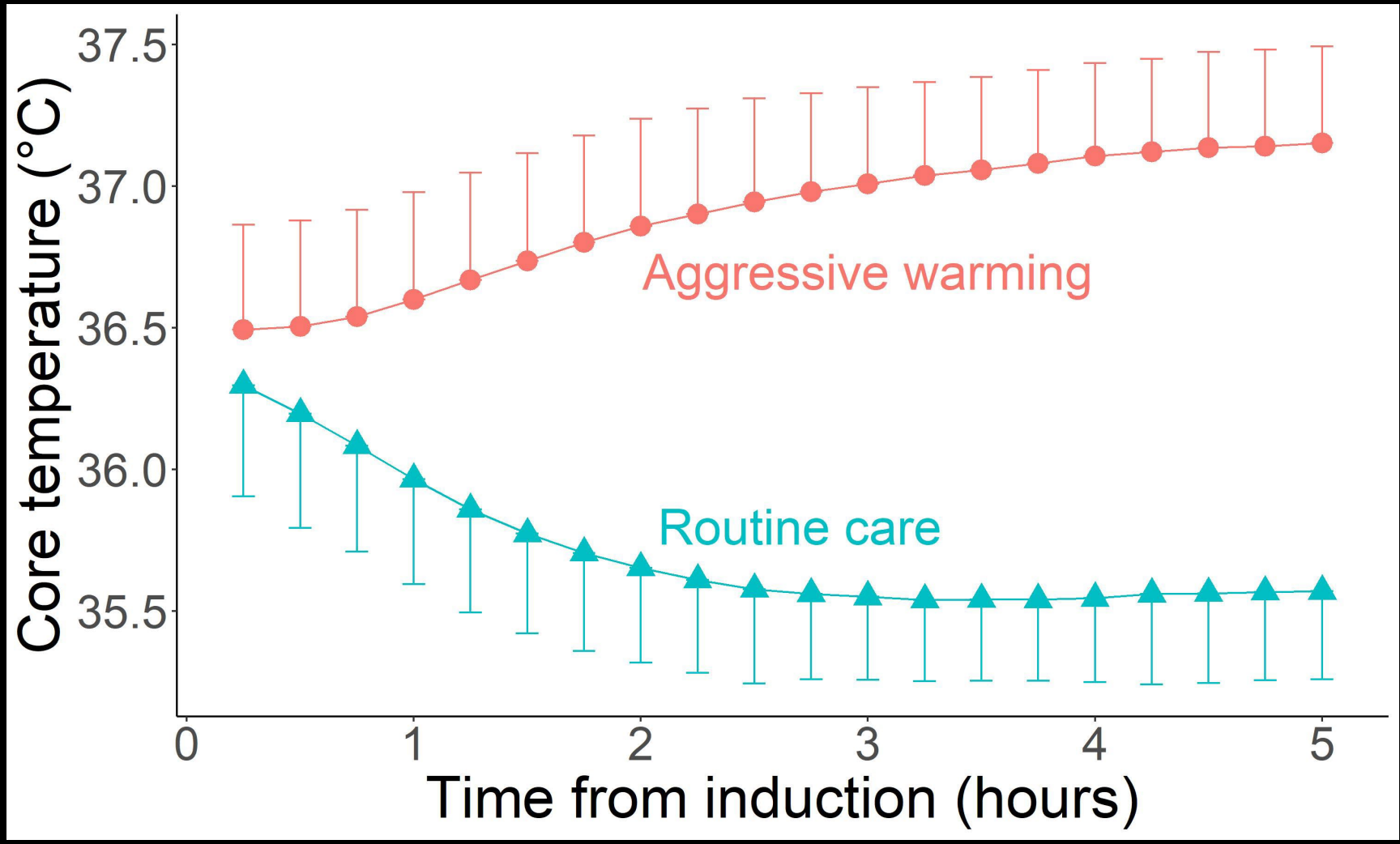
- CDC definitions

Transfused red cell volume

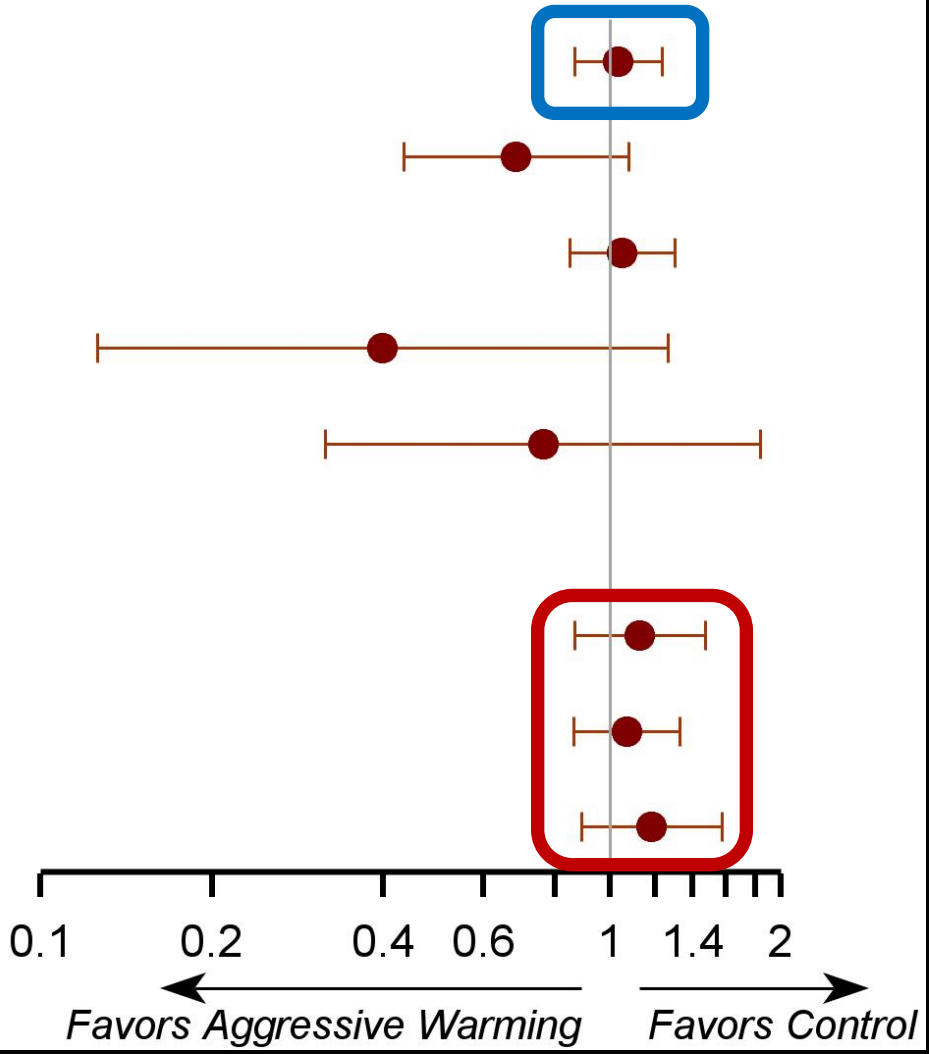


>99% 30-day follow-up

Excellent Thermal Management

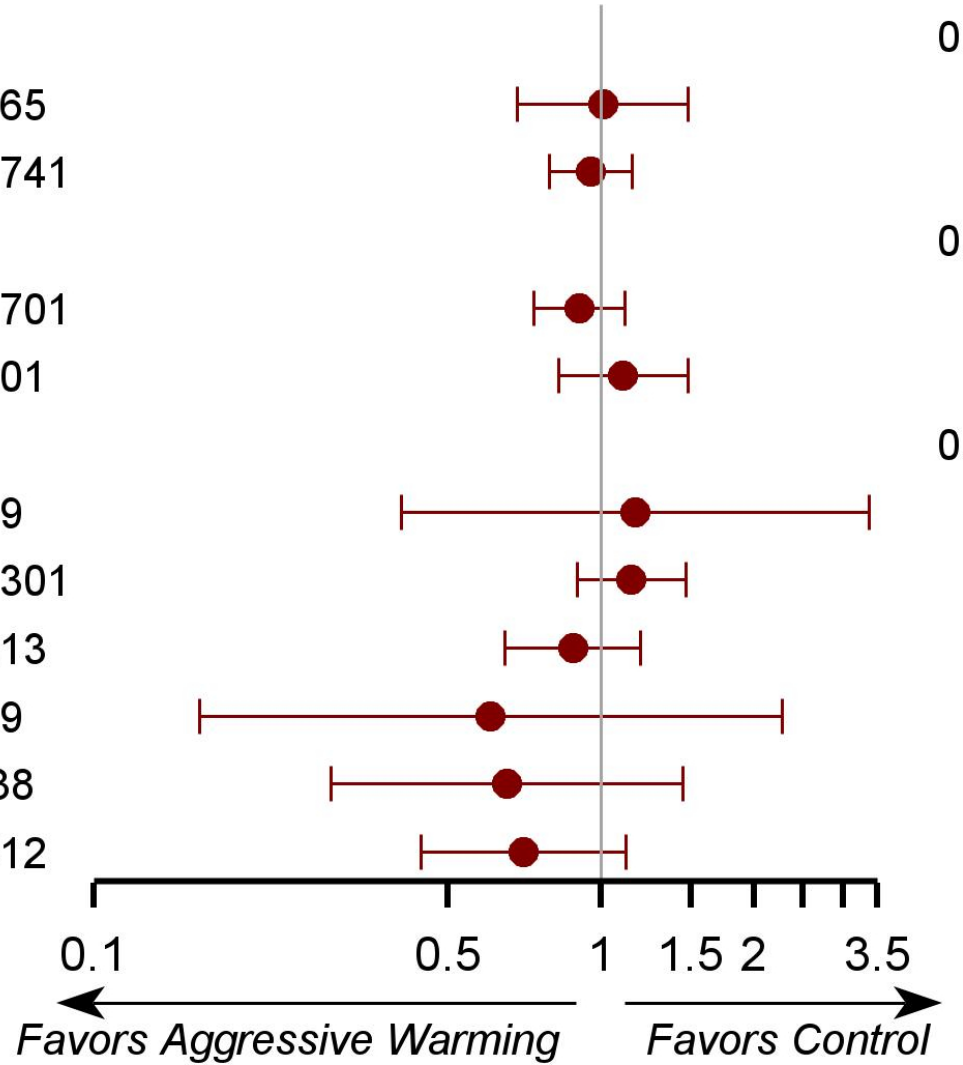


	Aggressive Warming (n/N)	Routine Care (n/N)
Primary outcomes		
Common effect	246/2497	239/2490
Average relative effect		
- MINS	233/2470	223/2468
- Non-fatal cardiac arrest	6/2493	15/2486
- Mortality	13/2489	17/2482
Secondary outcomes		
Surgical site infection	178/2487	157/2479
Transfusion requirement	254/2494	236/2486
Hospital readmission	161/2462	135/2447



Primary outcome

Subgroup	Aggressive Warming (n/N)	Routine Care (n/N)	P-value
Age			0.81
<65 years	48/753	51/765	
≥65 years	198/1754	188/1741	
Sex			0.29
Male	169/1668	156/1701	
Female	77/836	83/801	
Surgery type			0.37
Orthopedic	6/56	6/49	
Laparoscopic	110/1313	121/1301	
Open abdominal	75/610	71/613	
Neurosurgical	7/126	3/89	
Urologic	14/138	9/138	
Other	34/261	29/312	



Randomization to 37 v. 35.5° C Core Temp

Does not reduce cardiovascular composite

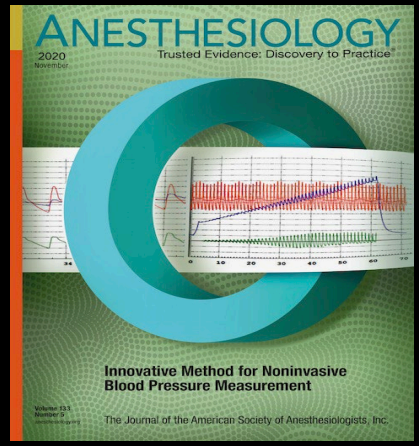
- Individually only powered for myocardial injury

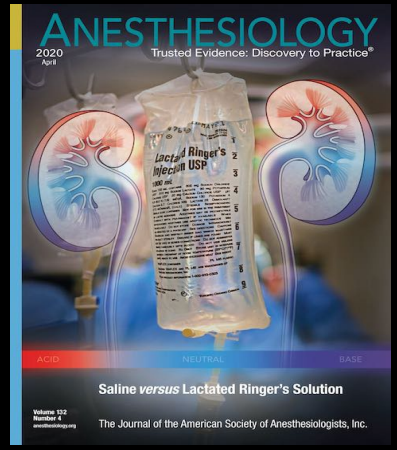
Does not reduce

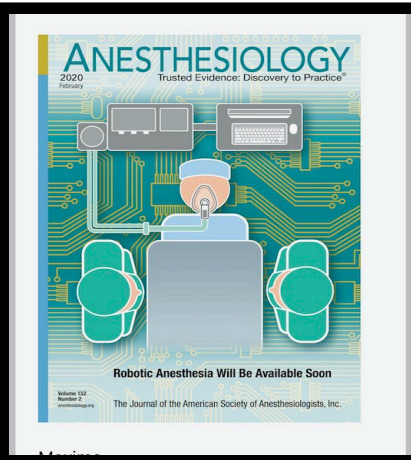
- Surgical site infections
- Transfusion requirement
- Duration of hospitalization or readmissions

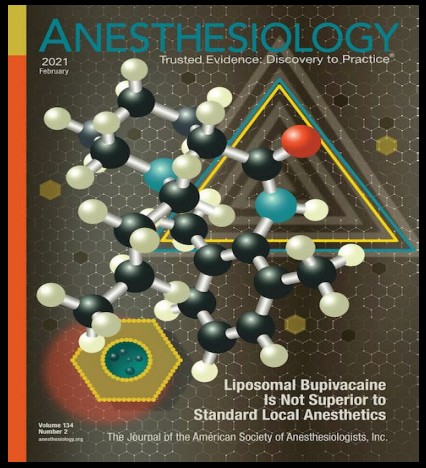
Intraop temps ≥35.5° C appear to be safe

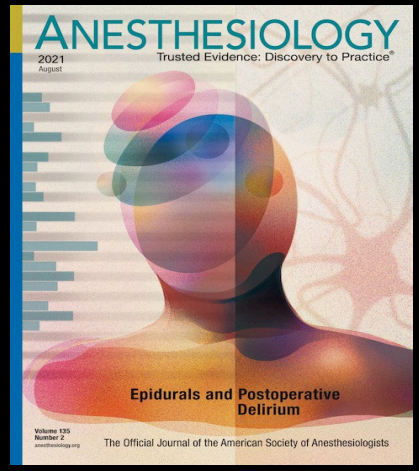
And that's all folks…

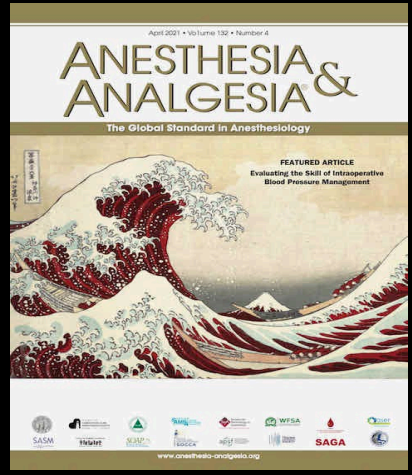


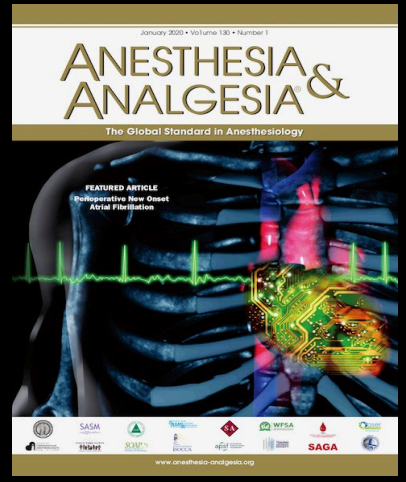


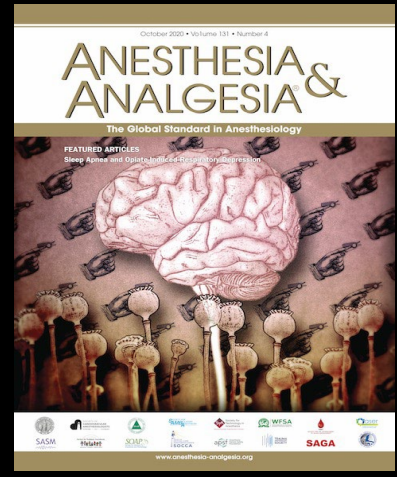










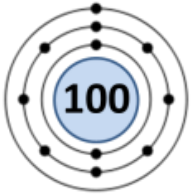


Selected Outcomes Research covers since 2020

Canadian VIGOUR Centre
Bridging Hearts and Minds

Study of Dietary Intervention Under 100 MMOL in Heart Failure

SODIUM-HF



Justin A. Ezekowitz, MBBCh MSc, on behalf of the SODIUM-HF investigators

Professor, University of Alberta
Co-Director, Canadian VIGOUR Centre
Cardiologist, Mazankowski Alberta Heart Institute
ACC 2022

@sodiumhf

- Funding from:

University Hospital Foundation

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SODIUM-HF team

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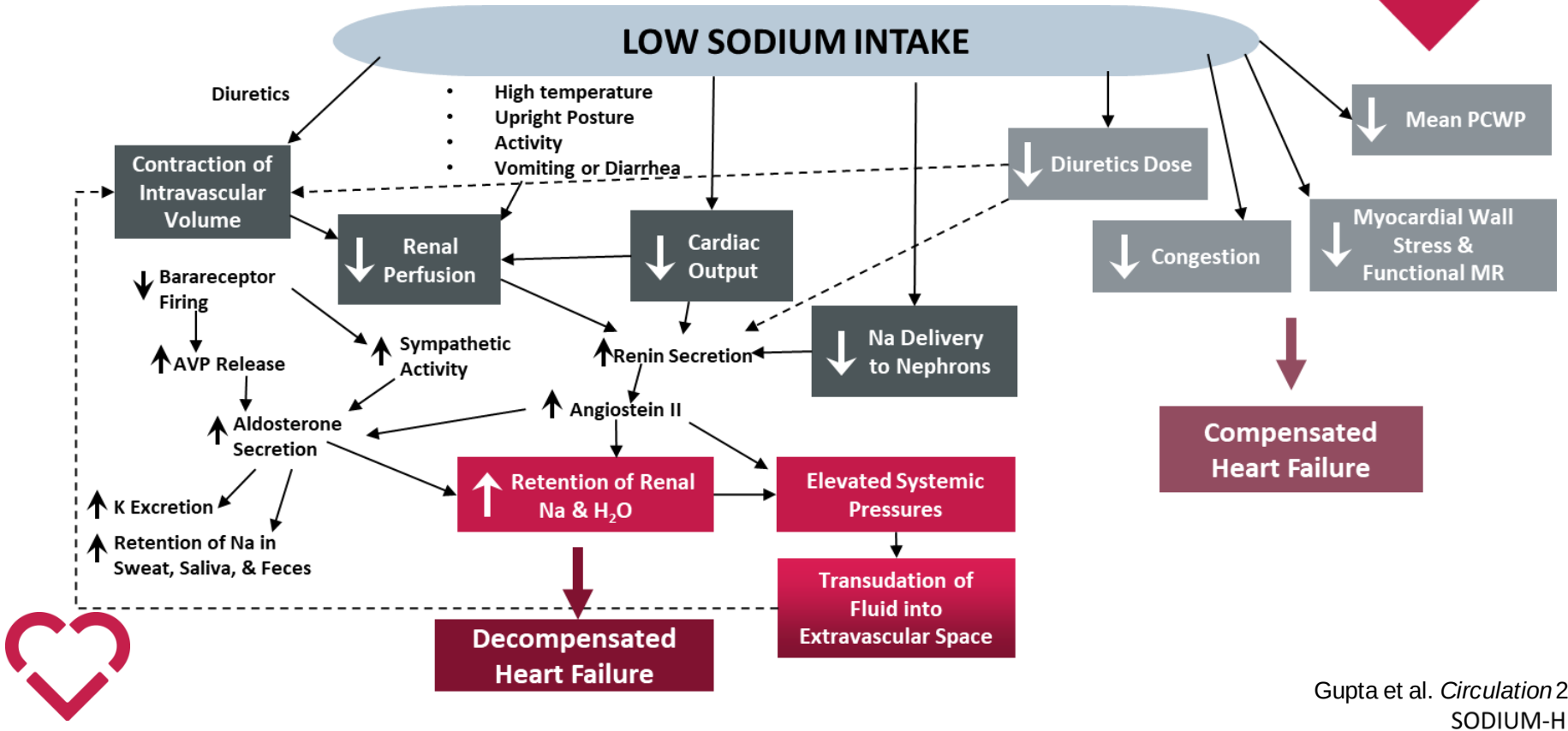
Heart Failure and Dietary Sodium

- HF is associated with:
  - neurohormonal activation
  - abnormalities in autonomic control
  - sodium and water retention
- Clinicians have focused on dietary sodium and water restriction to minimize the risk of volume overload for > 100 years
- Little evidence supports this practice

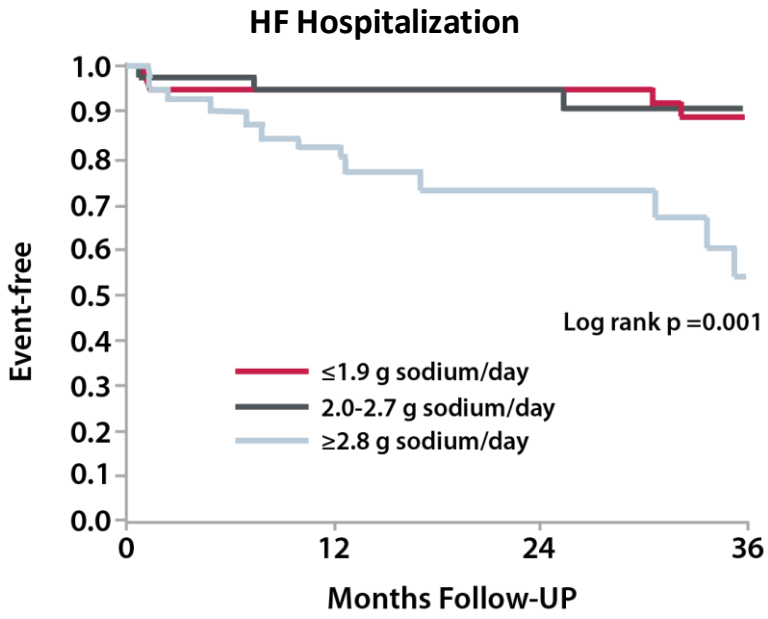
SODIUM-HF

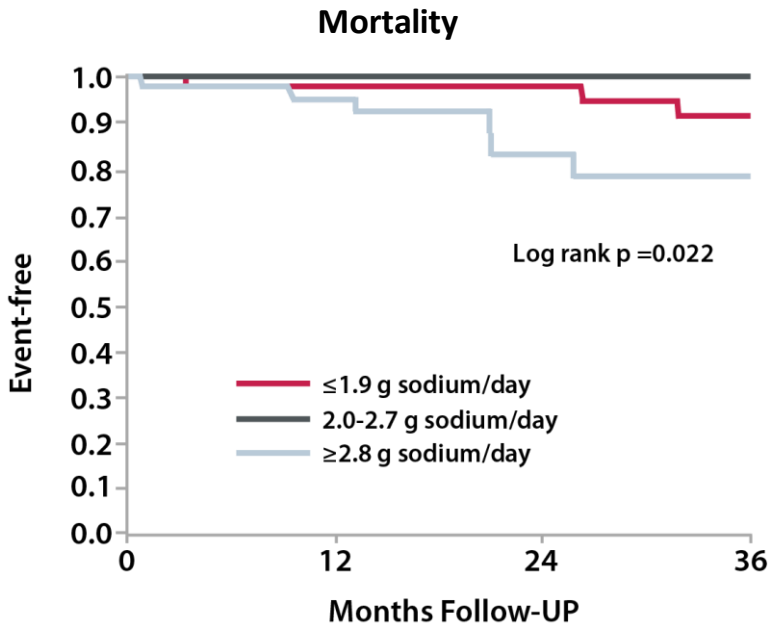
Dietary Sodium Intake



Gupta et al. *Circulation* 2012

Dietary sodium: Observational studies





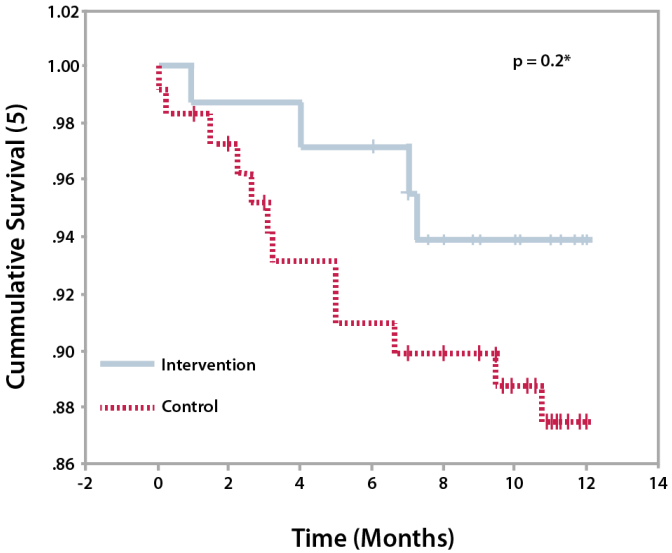
n= 123 patients with HF

Arcand et al. *Am J Clin Nutr.* 2011.

SODIUM-HF

Dietary sodium reduction: RCT

n= 195 patients with HF, Outpatient, Mexico city



Intervention group: Dietary recommendations for sodium restriction to <2400 mg/day provided by a dietitian.
Control Group: Usual dietary recommendations for dietary sodium reduction.

Colin et al. *Rev Chil Nutr*, 2010.

<u>Systematic review:</u>
9 studies
All < 100 patients
Mixed interventions

No consistent results on any outcome

Mahtani *JAMA: Internal Medicine* 2018

SODIUM-HF Objectives

Evaluate the effects of a low-sodium diet, compared to usual care, in patients with HF, on a 12 month outcome of:

- **Primary Endpoint:** Composite clinical outcome of All-cause mortality, CV hospitalizations, CV ED visits

- **Secondary Endpoints:**
  - Quality of life (by KCCQ)
  - Exercise capacity (by 6MWT)
  - NYHA class

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

University Hospital Foundation

SODIUM-HF: Trial Design

841 patients with heart failure (NYHA II-III) on optimally tolerated medical therapy

Eligible patients identified via inclusion/exclusion criteria

Participants provide written consent and complete a baseline evaluation

RANDOMIZATION (open label)

- **1500 mg/day Na**
- **Usual care**

Clinical visits (12 months) and phone follow-up (12 months)

Primary Endpoint:

Composite outcome of all-cause mortality, CV hospitalizations, or CV ED visits

Secondary Endpoints:

Change in KCCQ, 6-minute walk test, and NYHA class

Colin-Ramirez, *AHJ*, 2018

SODIUM-HF

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SODIUM-HF: Sites

SODIUM-HF

26 sites

Canada, Mexico, Chile, Colombia, Australia, New Zealand

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SODIUM-HF: In/Exclusion criteria

SODIUM Inclusion Criteria

- ✓ 18 years or older and willing/able to sign informed consent.
- ✓ Confirmed diagnosis of HF (both reduced and preserved systolic function eligible)
- ✓ NYHA Class II-III
- ✓ On optimally tolerated medical therapy according to CCS guidelines

SODIUM Exclusion Criteria

- ✗ Patients with an average dietary intake of <1500 mg Na/day
- ✗ Serum sodium <130 mmol/L
- ✗ Hemodialysis-dependent chronic renal failure (or glomerular filtration rate <20 mL/min)
- ✗ Uncontrolled thyroid disorder or end-stage hepatic failure
- ✗ Cardiac device or revascularization procedure in previous month or planned in the next 3 months
- ✗ Hospitalization due cardiovascular causes in the previous 1 month
- ✗ Uncontrolled atrial fibrillation (resting heart rate >90 bpm)
- ✗ Active malignancy with an expected life expectancy <2 years
- ✗ Another comorbid condition or situation which could preclude compliance with the protocol
- ✗ Enrolled in another interventional research study

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SODIUM-HF: Intervention

Patients randomized to one of two study arms:

1. Low-sodium containing diet
    - <1500 mg daily (<65 mmol/daily)

2. Usual care
    - general advice to limit dietary sodium as provided in routine clinical practice

SODIUM-HF: Intervention

- Samples of **menus** at different levels of energy requirement (1400-2200 kcal)
- Patient might **interchange** any of the food items included in the menus by another one included in the recommended foods lists of the same food group that the original one included in the menu.
- Food **individualized** to local region/country
- If energy requirements were adjusted during a follow-up visit, new sample menus were provided.
- **3 day food records** for each visit

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Colin-Ramirez, *AHJ*, 2018
Colin-Ramirez, *CJC Open*, 2019

SODIUM-HF: Sample Size / DMC

- Sample size:
  - Based on the primary composite outcome
  - Expected event rate of 25% in usual care arm
  - **30%** reduction in the primary outcome
  - **80%** power, two-sided type I error rate of 0.05
  - Total enrollment of **992** patients

- The Data Monitoring Committee
  - Reviewed data from the first **500** participants with complete 12-month follow-up
  - Mandate was to advise on *futility* (if conditional power was <20%) or *efficacy* (two-sided p-value <0.001).
  - This review, in addition to an assessment of trial operational feasibility and the impact of the COVID-19 pandemic, led to an early stopping with the last patient enrolled on December 09, 2020 and complete 12 month follow-up in December 2021.

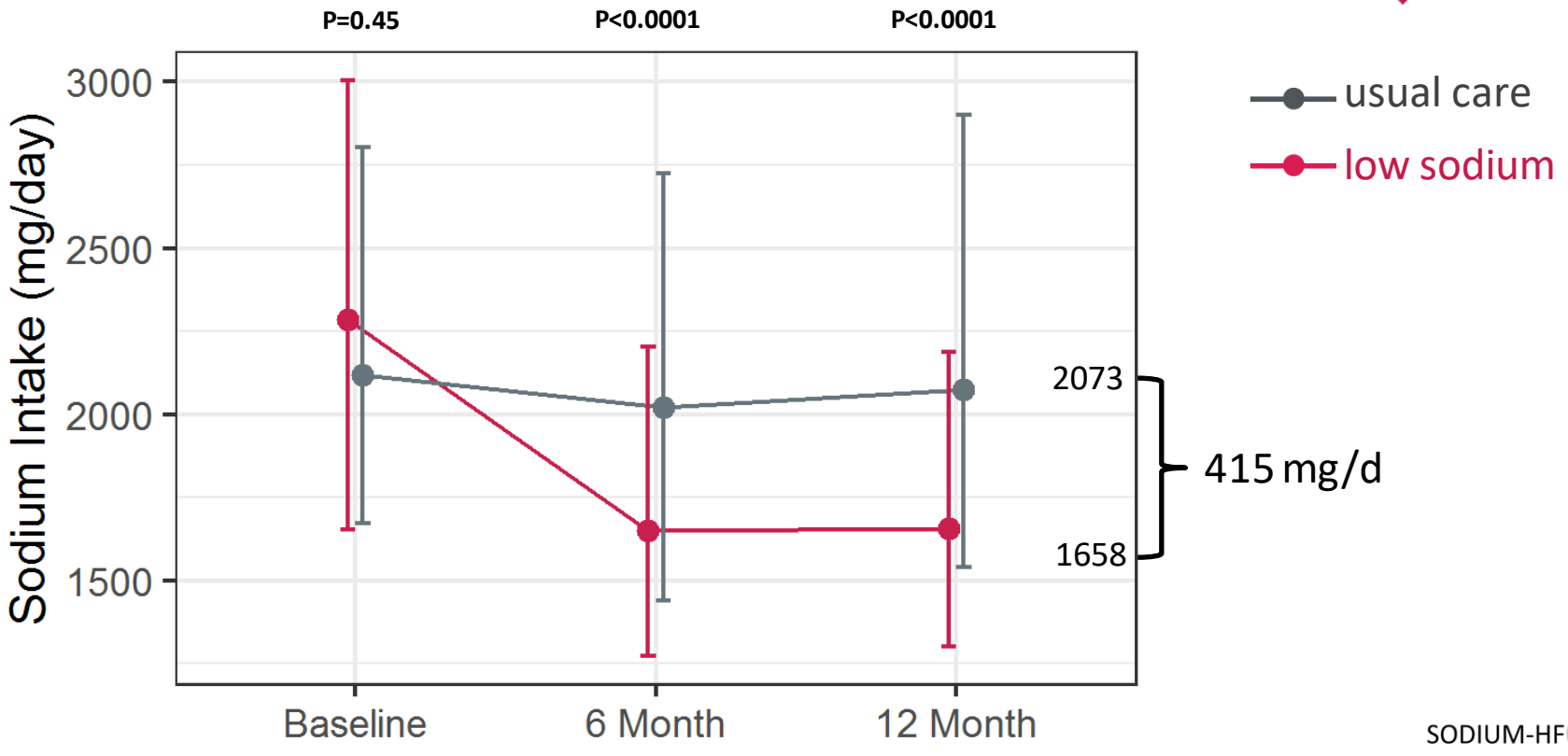
SODIUM-HF: Baseline Characteristics

	Low sodium diet group n=397	Usual care group n=409
Age, years	66 (57–73)	67 (58–75)
Female Sex	127 (32%)	141 (34%)
Geographical region		
Canada	230 (58%)	241 (59%)
Australia and New Zealand	79 (20%)	78 (19%)
Mexico, Chile, and Colombia	88 (22%)	90 (22%)
Diagnosed with HF for ≥1 year	269 (68%)	282 (69%)
Hospitalised for HF in past 12 months	129 (32%)	141 (34%)
Ejection fraction	36 (28–48)	35 (27–50)

SODIUM-HF: Baseline Characteristics

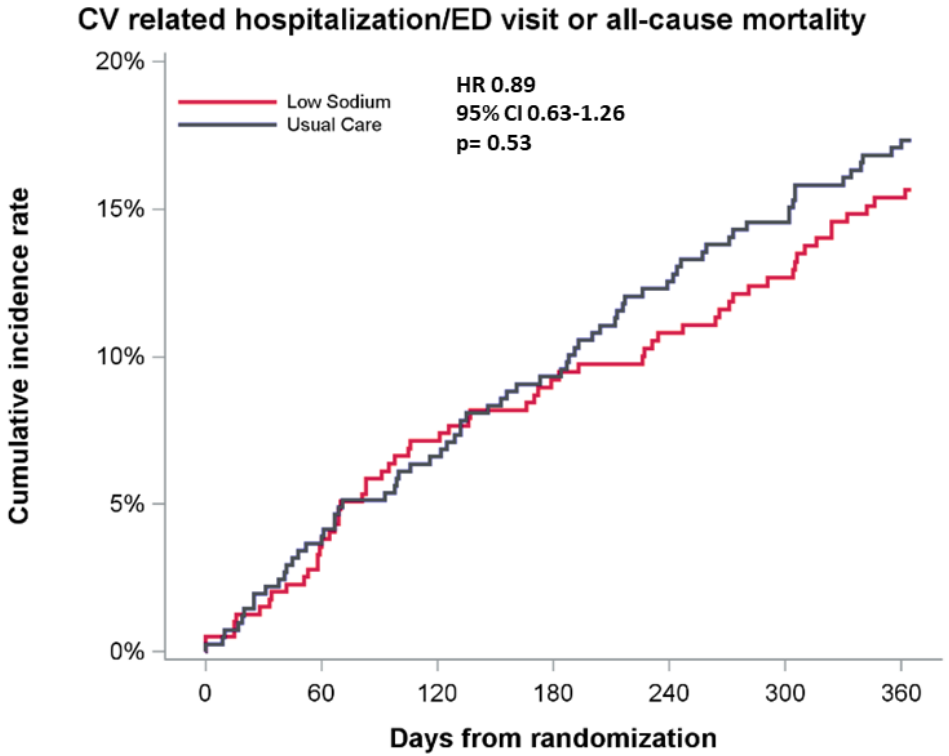
	Low sodium diet group n=397	Usual care group n=409
Medical history		
Coronary artery disease	187 (47%)	186 (45%)
Atrial fibrillation or flutter	156 (39%)	173 (42%)
Diabetes (type 1 or 2)	132 (33%)	156 (38%)
Vital signs and physical findings		
BMI, kg/m²	30 (26–35)	31 (27–36)
Heart rate, beats per min	69 (61–76)	69 (61–77)
Systolic blood pressure, mm Hg	118 (105–129)	118 (104–130)
Laboratory values		
eGFR, mL/min per 1·73m²	61 (46–75)	58 (42–71)

Dietary sodium intake



Outcomes

Primary Outcome



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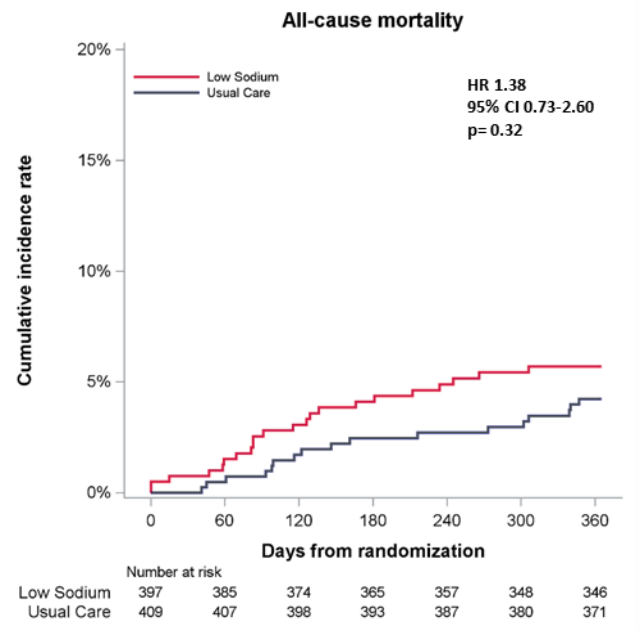
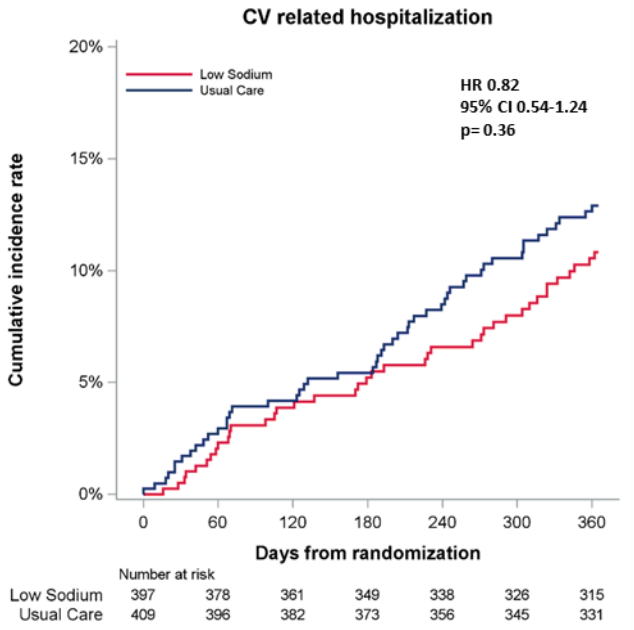
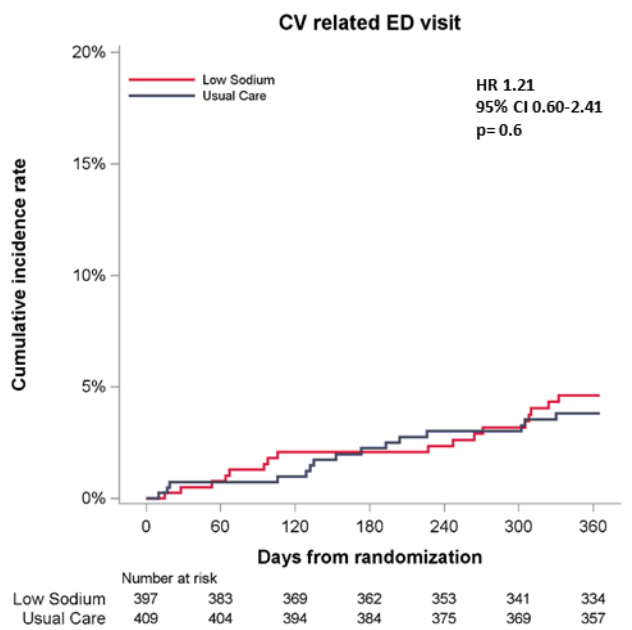
Secondary Outcomes







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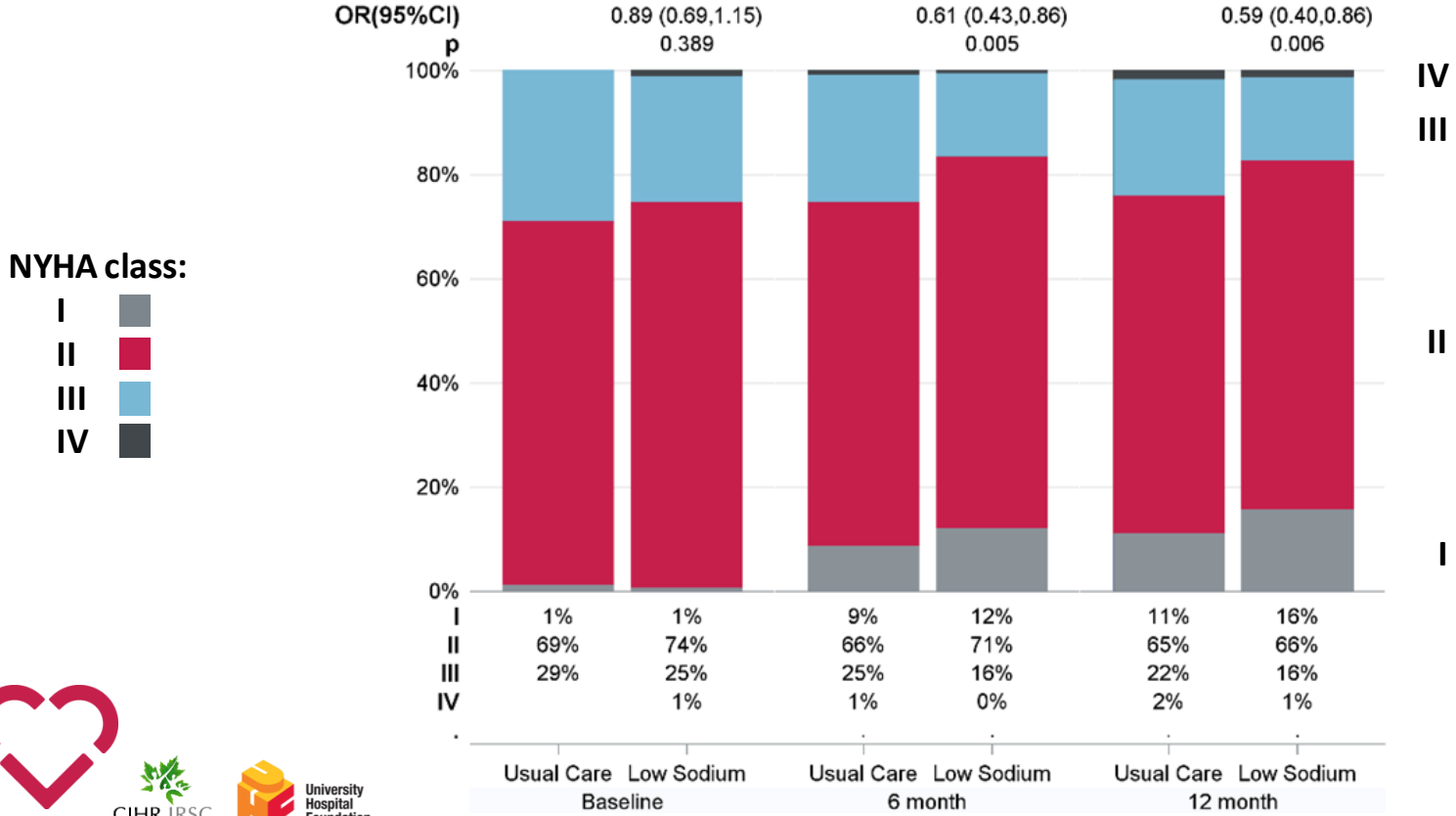
SODIUM-HF

Change in NYHA class



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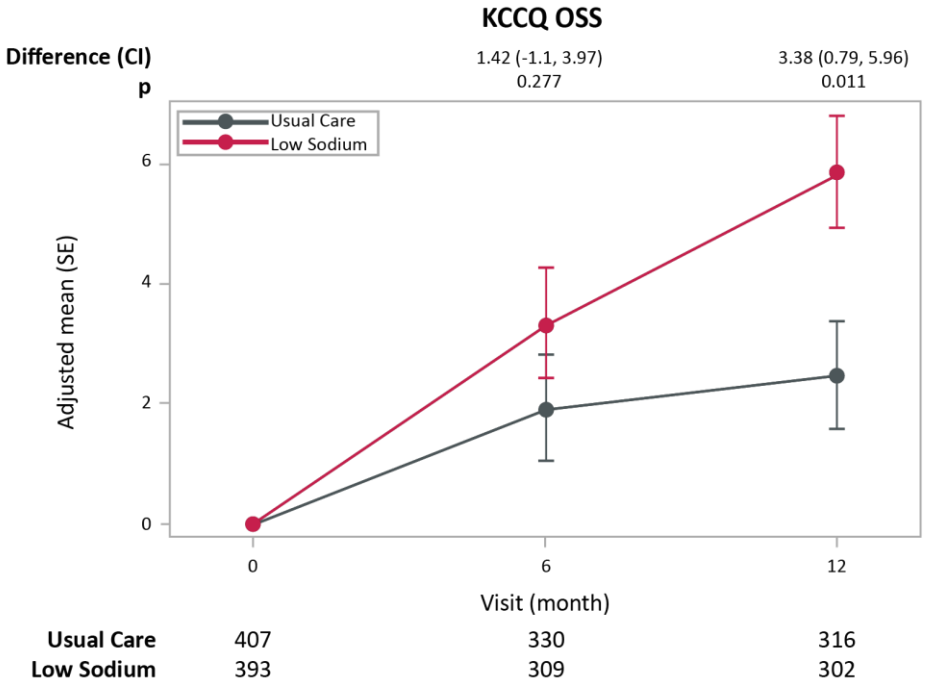
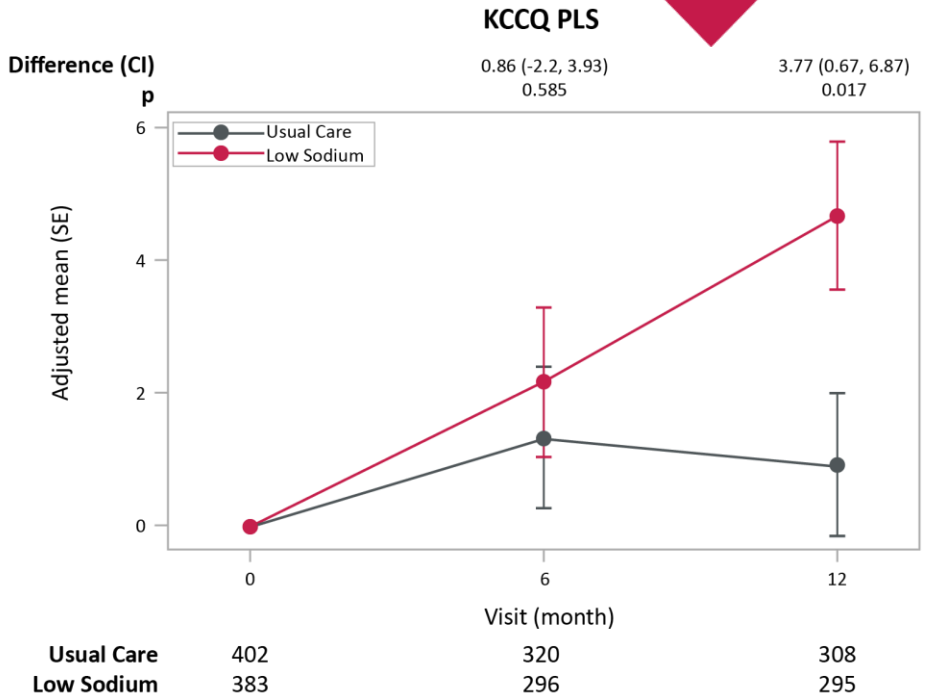
Change in KCCQ score





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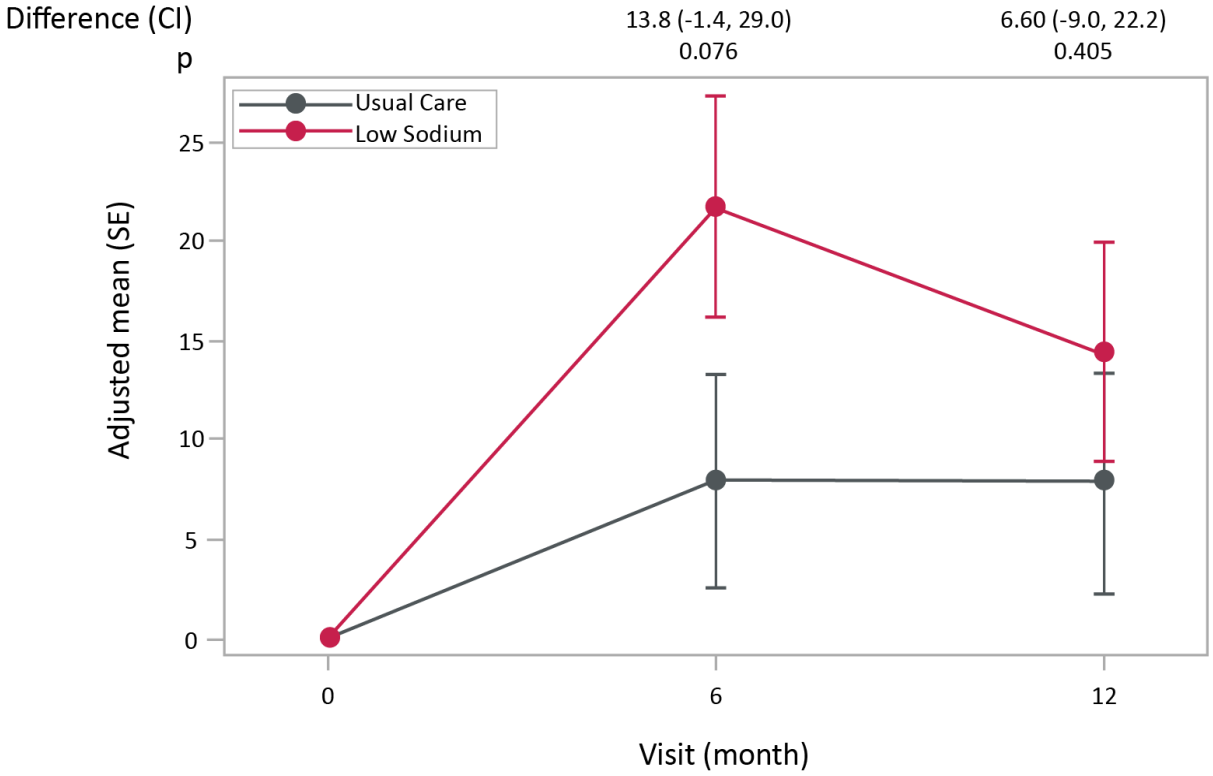
Change in 6 min walk test distance



Usual Care	332	215	191
Low Sodium	328	204	199

Limitations

- There was a sodium reduction of 415 mg / day by 12 months, and greater reductions in daily sodium or alternatively, enrolling patients with markedly higher dietary sodium may or may not produce different results.
- The trial was stopped early
- Lower than anticipated event rate
- Inclusion criteria were pragmatic and no NT-proBNP required

Conclusions

1. In ambulatory patients with HF, a dietary intervention to reduce sodium intake did not reduce clinical events.
2. There was a modest benefit on quality of life as measured by the KCCQ, and in NYHA class.
3. The 6-minute walk test was not statistically different between groups.

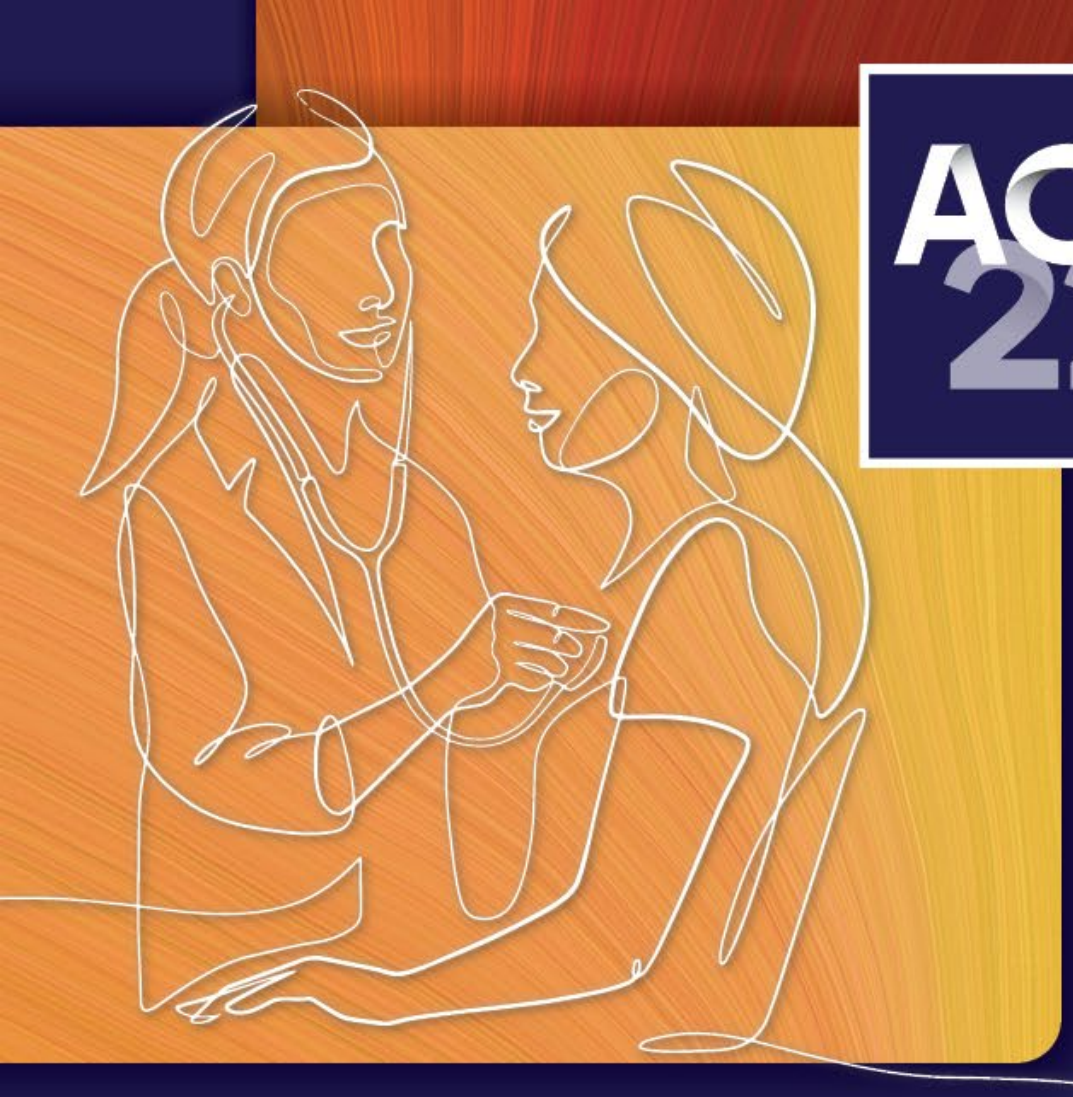
Implications

A low-sodium diet as done in SODIUM-HF:

- Clinicians: as a therapy to improve QOL
- Patients: as part of an overall health strategy
- Guidelines: informs with best evidence

SODIUM-HF Participants

- A special thank you to those patients who volunteered their time and effort to participate in the SODIUM-HF trial



ACC 22

A Randomized Controlled Trial of Influenza Vaccine to Prevent Adverse Vascular Events (IVVE)

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TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

Background

- Influenza increases the risk of CV events and deaths
- A lower rate of CV events related to ischemia and death has been reported with influenza vaccination
- 80% of CV disease burden occurs in LMICs where use of influenza vaccine is extremely low

Trial Design

- A pragmatic, double-blind, randomized trial comparing inactivated influenza vaccine to placebo, to prevent CV outcomes in ten countries in Asia, the Middle East, and Africa over three influenza seasons
- Use of a placebo was in keeping with WHO criteria for vaccine trials in LMICs, participants allowed to use influenza vaccine outside of the trial

Eligibility

- Patients aged ≥ 18 years with a clinical diagnosis of heart failure and NYHA functional class II, III and IV

- Excluded:
- - Anaphylactic reaction to a previous dose of TIV
- - Known IgE-mediated hypersensitivity to eggs
- - GBS within 8 wks of previous influenza vaccine
- - Anaphylactic reaction to neomycin
- -Influenza vaccine in 2 of 3 previous years
- - Severe valvular disease where repair or replacement considered

Study Vaccines

- 0.5 ml IM dose of inactivated influenza vaccine (VAXIGRIP□ vaccine, TIV or QIV if available)
- Placebo (0.5 ml saline)

- Administered annually for 3 influenza seasons

Co-Primary Outcomes

- First Primary Outcome: composite of CV death, non-fatal MI, and non-fatal stroke

- Second Primary: First Co-Primary and heart failure hospitalizations

Secondary Outcomes

- Components of Primary
  - Non-fatal MI
  - Non-fatal Stroke
  - CV deaths
- All hospitalizations
- Pneumonia
- All deaths

Sample size

- 5,000 participants, 80% power to detect reduction in primary composite from 17% in the control group to 14% in the vaccine group

Primary Analysis

- Events (irrespective of influenza circulation) were analysed by ITT for the first and second primary composite outcomes
- Step-down fall-back approach, first primary composite (time to first event) at two-sided alpha 0.04, if not significant, second primary (recurrent events) tested at 0.01

Secondary Analysis

- Time to event for secondary outcomes
- Recurrent hospitalizations for heart failure and recurrent all-cause hospitalizations
- Analysis of events that occurred during peak influenza circulation and outside of them

Baseline Characteristics

	Influenza vaccine (n=2560)	Placebo (n=2569)
Age (yrs)	57.4±15.1	57.0±15.6
Heart rate	80.3±15.1	80.3±14.9
Systolic BP	125.8±23.3	125.6±24.1
Female	1333 (52.1)	1305 (50.8)
Region		
China	348 (13.6)	346 (13.5)
India	583 (22.8)	588 (22.9)
Africa	1023 (39.9)	1028 (40.0)
Philippines	359 (14.0)	359 (14.0)
Middle East	247(9.6)	248 (9.7)

Heart Failure

	Influenza vaccine (n=2560)	Placebo (n=2569)
NYHA Class		
II	1773 (69.3)	1790 (69.7)
III	683 (26.7)	657 (25.6)
IV	104 (4.1)	122 (4.7)
LV Function		
Preserved (>50%)	560 (21.9)	597 (23.2)
Mild (LVEF 40-49%)	441 (17.2)	422 (16.4)
Mod (LVEF 31-39%)	621 (24.3)	629 (24.5)
Severe (LVEF ≤30%)	821 (32.1)	800 (31.1)

Co-Morbidity

	Influenza vaccine (n=2560)	Placebo (n=2569)
Prior stroke	202 (7.9)	207 (8.1)
Prior MI	546 (21.3)	514 (20.0)
COPD	136 (5.3)	121 (4.7)
Hypertension	1661 (64.9)	1668 (64.9)
CKD	176 (6.9)	167 (6.5)
Diabetes	570 (22.3)	590 (23.0)
Hyperlipidemia	419 (16.4)	427 (16.6)
Atrial fibrillation	248 (9.4)	282 (10.4)

Medications

	Influenza vaccine (n=2560)	Placebo (n=2569)
Beta blocker	1545 (60.4)	1550 (60.3)
ACE inhibitor or ARB	1853 (72.3)	1835 (71.4)
Aldosterone inhibitor	1232 (48.1)	1207 (47.0)
Other Diuretics	1702 (66.5)	1681 (65.4)
Long-acting nitrate	370 (14.5)	388 (15.1)
Digoxin	597 (23.3)	588 (22.9)
Aspirin or thienopyridines	1543 (60.2)	1534 (59.7)
Vitamin K antagonists	263 (10.3)	242 (9.4)
Direct oral anticoagulants	35 (1.4)	38 (1.5)

First Events by Study Group

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95% CI)	P value
First primary	380 (14.8)	410 (16.0)	0.93 (0.81-1.07)	0.30
Second primary	520 (20.3)	568 (22.1)	0.91 (0.81-1.03)	0.13
All deaths	427 (16.7)	473 (18.4)	0.90 (0.79-1.03)	0.13
CV death	334 (13.0)	374 (14.6)	0.89 (0.77-1.04)	0.13
Non-CV death	93 (3.6)	99 (3.9)	0.94 (0.71-1.25)	0.68
Non-fatal MI	21 (0.8)	23 (0.9)	0.91 (0.50-1.65)	0.76
Non-fatal Stroke	47 (1.8)	43 (1.7)	1.10 (0.73-1.66)	0.66

First Events by Study Group

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95% CI)	P value
All Hosp	387 (15.1)	453 (17.6)	0.85 (0.74-0.97)	0.01
HF Hosp	241 (9.4)	274 (10.7)	0.88 (0.74-1.04)	0.14
Pneumonia	61 (2.4)	104 (4.0)	0.58 (0.42-0.80)	0.0006

Recurrent Events by Study Group

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95%CI)	P
Second primary	798 (25.4)	900 (27.8)	0.92 (0.83-1.02)	0.11
All Hosp	536 (17.1)	631(19.5)	0.84 (0.75-0.94)	0.002
HF Hosp	354 (11.3)	374 (11.6)	0.93 (0.81-1.08)	0.36

First Events during Peak Influenza Season and Non-Peak Period

	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	HR (95% CI)	Influenza vaccine	Placebo	HR (95% CI)
First Primary	193 (7.7)	227 (9.4)	0.82 (0.68-0.99)	187 (7.5)	173 (6.9)	1.08 (0.88-1.33)
Second Primary	268 (10.7)	306(12.2)	0.87 (0.74-1.03)	252 (10.2)	262 (10.5)	0.96 (0.81-1.14)

First Events during Peak Influenza Season and Non-Peak Period

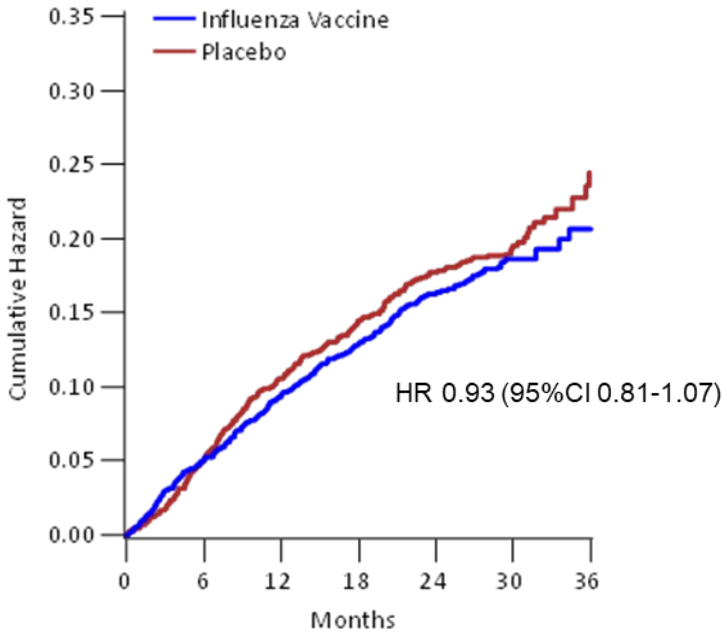
	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	HR (95% CI)	Influenza vaccine	Placebo	HR (95% CI)
All death	212 (8.4)	269 (10.6)	0.79 (0.66-0.95)	215 (8.6)	204 (8.1)	1.05 (0.87-1.28)
CV death	170 (6.7)	221 (8.7)	0.77 (0.63-0.94)	164 (6.6)	153 (6.1)	1.07 (0.86-1.34)
Non CV death	42 (1.7)	48 (1.9)	0.88 (0.58-1.34)	51 (2.0)	52 (2.0)	1.00 (0.68-1.48)
Non-fatal MI	9 (0.4)	13 (0.5)	0.69 (0.29-1.61)	12 (0.5)	10 (0.4)	1.20 (0.52-2.77)
Non-fatal stroke	23 (0.9)	24 (0.9)	0.98 (0.55-1.74)	24 (1.0)	19 (0.8)	1.26 (0.69-2.31)

First Events during Peak Influenza Season and Non-Peak Period

	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	HR (95% CI)	Influenza vaccine	Placebo	HR (95% CI)
All Hosp	195 (7.8)	228 (9.1)	0.84 (0.70-1.02)	192 (7.8)	225 (9.1)	0.84 (0.70-1.02)
HF Hosp	126 (5.0)	122 (4.9)	1.03 (0.80-1.32)	115 (4.7)	152 (6.1)	0.75 (0.59-0.96)
Pneumonia	28 (1.1)	54 (2.1)	0.51 (0.32-0.81)	33 (1.3)	50 (2.0)	0.65 (0.42-1.01)

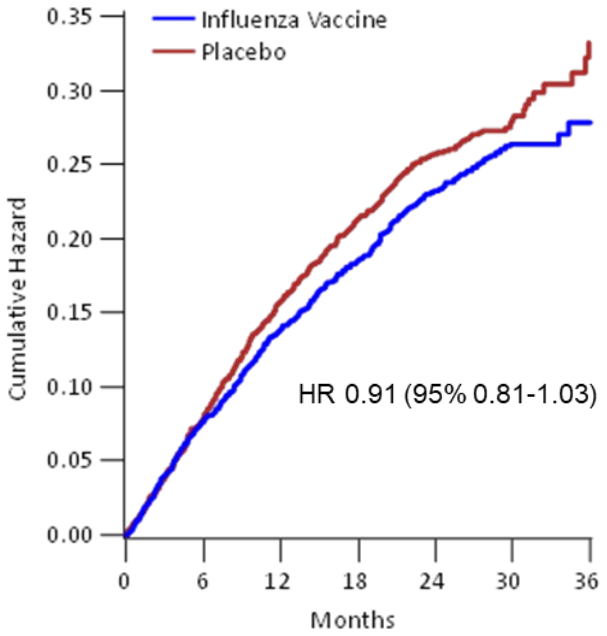
Kaplan Meier rates of the Primary Outcomes for First Events

A. *Primary Composite 1:* CV death, non-fatal myocardial infarction, or non-fatal stroke



No. at risk							
Infl. Vacc.	2560	2320	2112	1791	1551	490	98
Placebo	2569	2338	2099	1774	1547	489	115

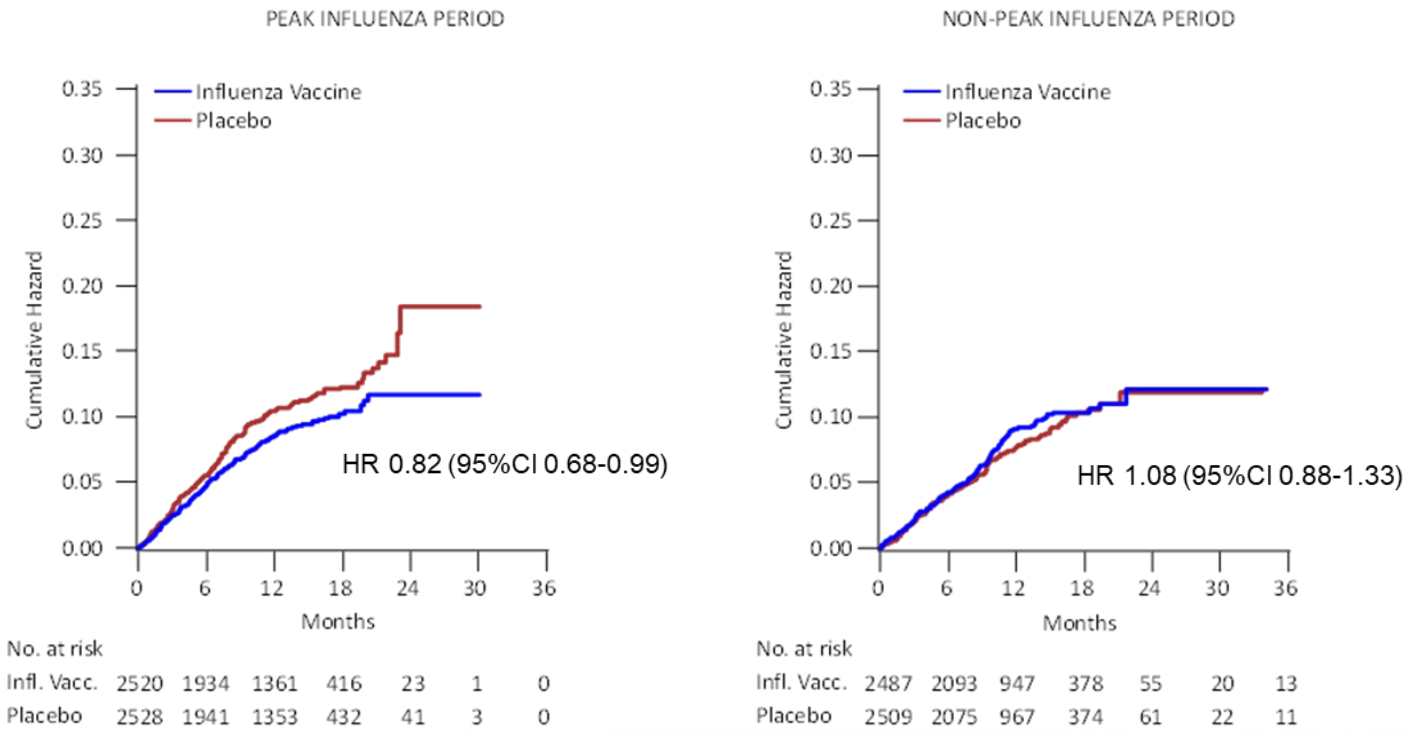
B. *Primary Composite 2*: CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure



No. at risk							
Infl. Vacc.	2560	2252	2019	1697	1454	445	89
Placebo	2569	2274	2019	1660	1439	426	99

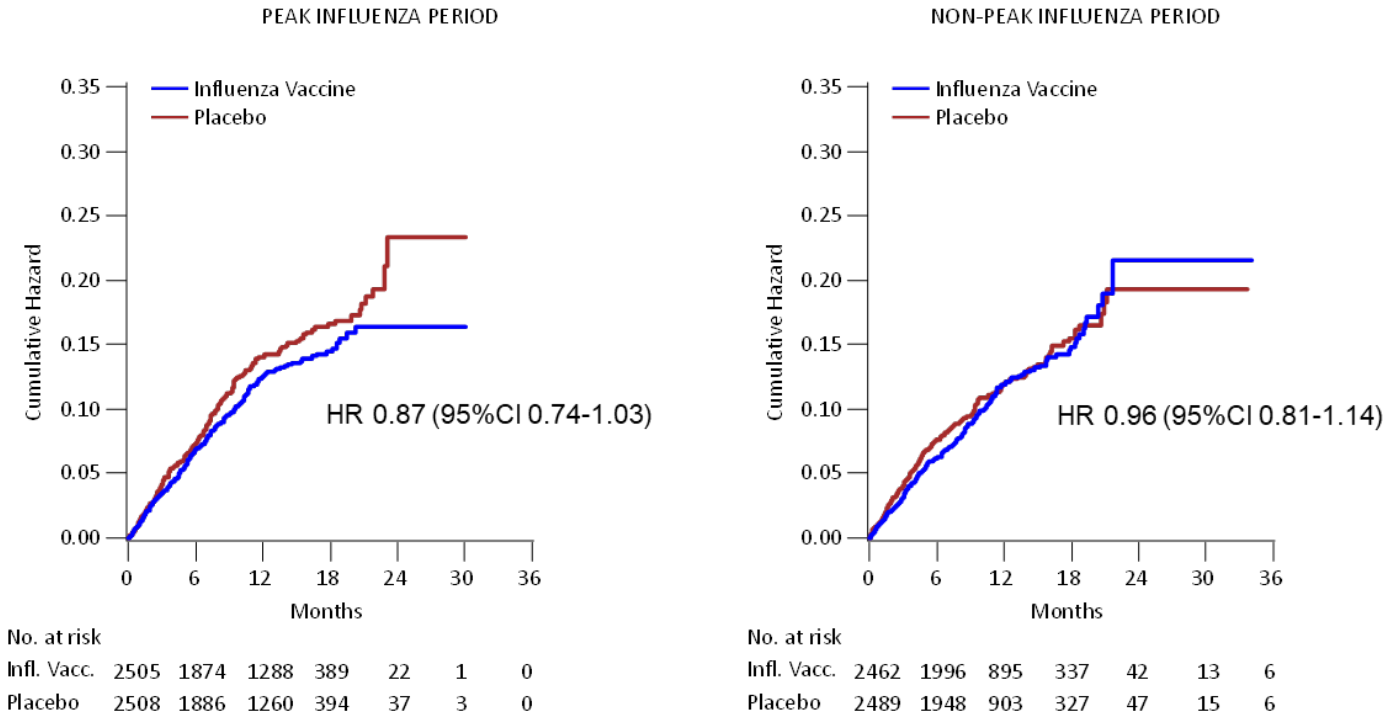
Kaplan Meier rates of the First Primary Outcome during Peak Influenza Period and Non-Peak Period

A. *Primary Composite 1:* CV death, non-fatal myocardial infarction, or non-fatal stroke



Kaplan Meier rates of the Second Primary Outcome during Peak Influenza

B. *Primary Composite 2:* CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure



Summary

- No significant difference in the primary outcomes between participants assigned to influenza vaccine versus placebo
- Secondary outcomes of pneumonia and hospitalization were reduced in the influenza vaccine group
- During periods of peak influenza circulation, there was a significant reduction in first primary outcome, deaths, and pneumonia in influenza vaccine group compared to placebo

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A Cluster Randomized *PR*agmatic Trial Aimed At Impr*O*ving Use Of Guideline Directed *M*edical Therapy In Out*P*atien*T*s With *H*eart *F*ailure: *PROMPT-HF*

Lama Ghazi MD PhD, Yu Yamamoto MS, Ralph Riello PharmD, Claudia Coronel-Moreno MPH, Melissa Martin MA, Kyle O'Connor MS, Michael Simonov MD, Joanna Huang PharmD, Temitope Olufade PhD MPH, James McDermott PhD, Ravi Dhar PhD, Silvio Inzucchi MD, Eric Velazquez MD, F Perry Wilson MD MSCE, Nihar Desai MD MPH, Tariq Ahmad MD MPH

Yale SCHOOL OF MEDICINE

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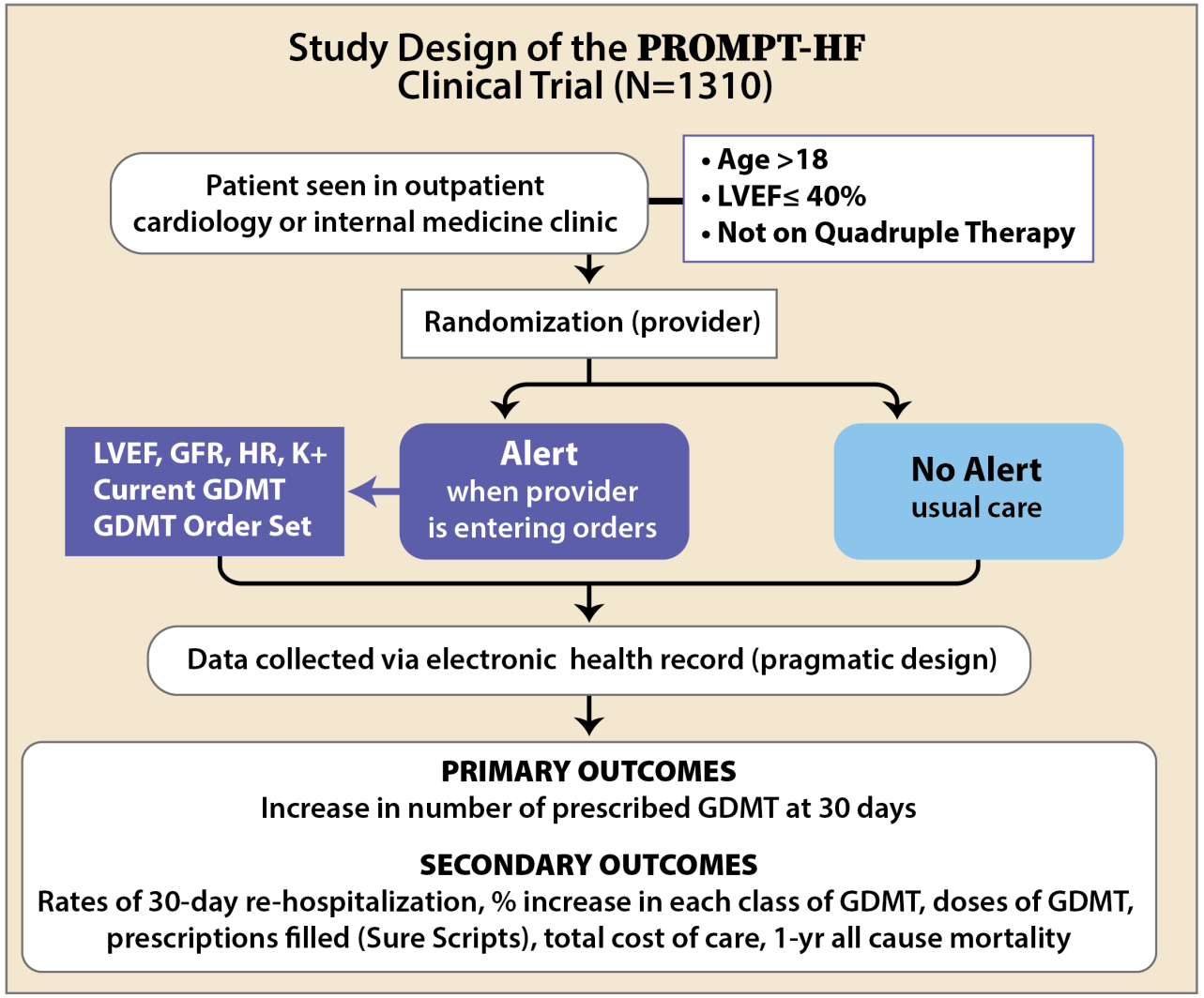
Background

- GDMT improves clinical outcomes in HFrEF but remains pervasively under-prescribed
- Efforts to optimize GDMT are abundant and resource intensive but limited evidence supports their use
- The electronic health record (EHR) may be used to target and individualize GDMT recommendations
- This approach is easily scalable and a low-cost way to accelerate high value care

Study Hypothesis

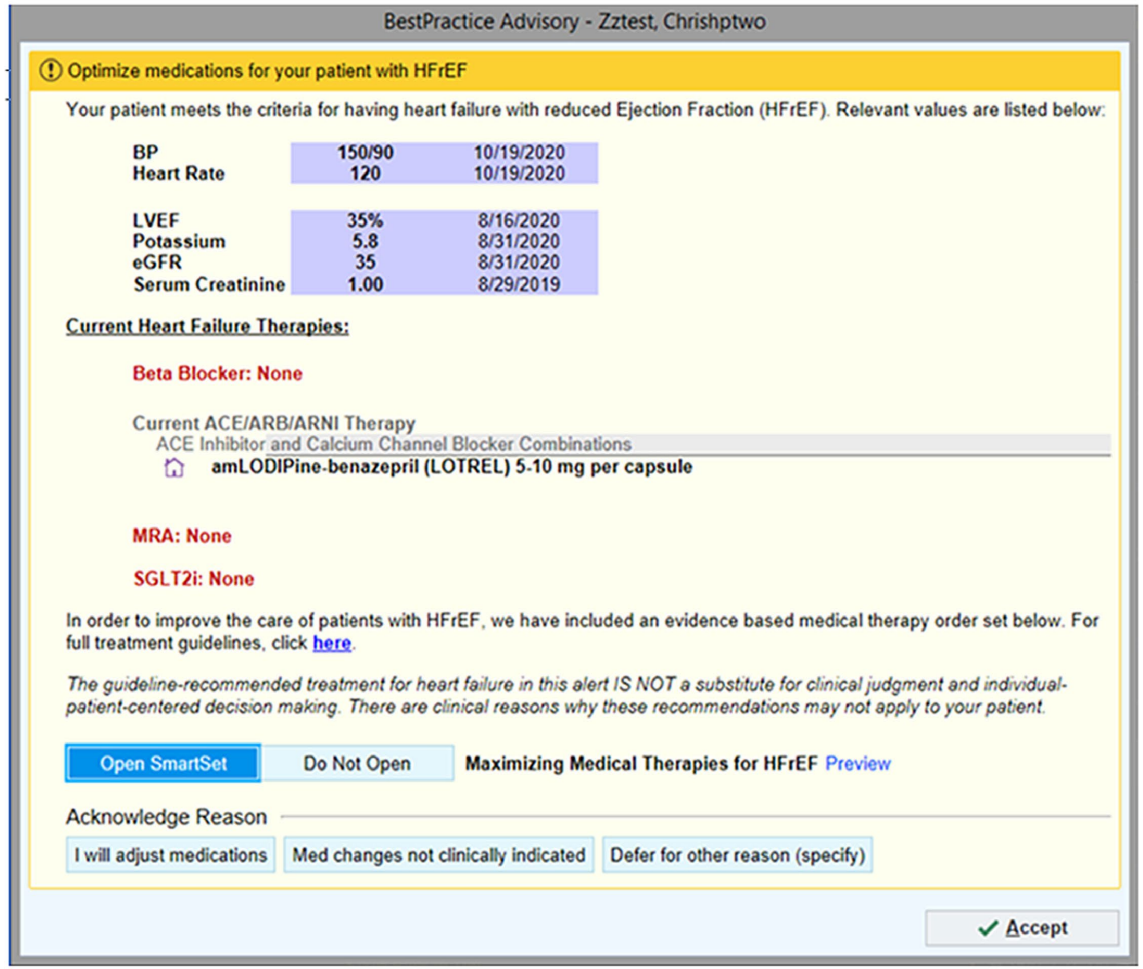
The ***PR***agmatic Trial ***O***f ***M***essaging to ***P***roviders about outpatient ***T***reatment of ***H***eart ***F***ailure (***PROMPT-HF***) was designed to test the hypothesis that **timely** and **targeted** alerting of recommendations about medical treatment of HFrEF tailored to the patient would lead to **higher** rates of GDMT prescription compared to usual care

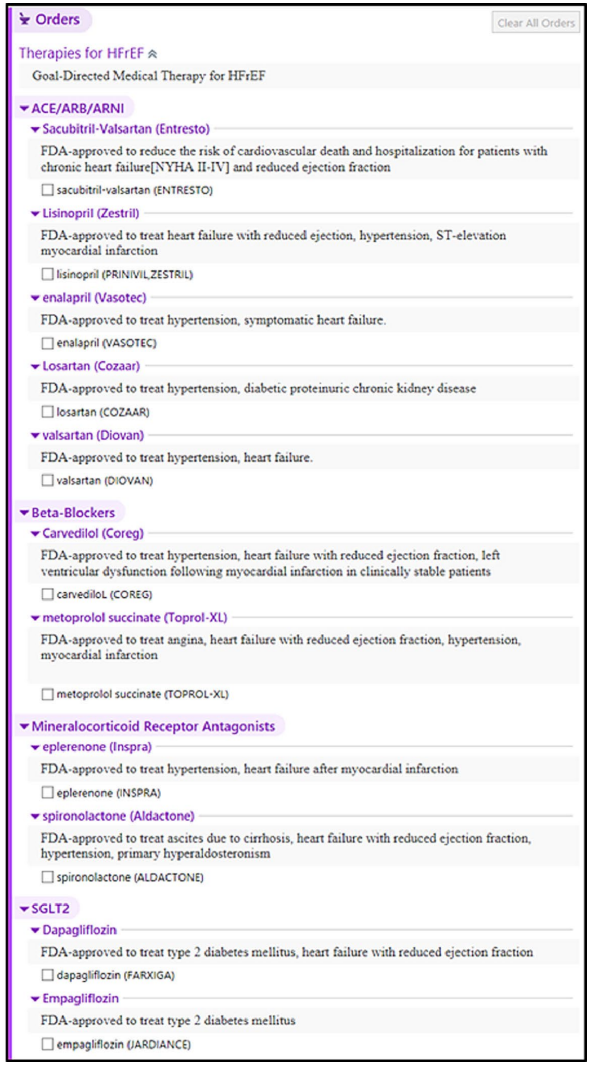
Study Design



Lama Ghazi et al. AHJ 2021; 9:409-419

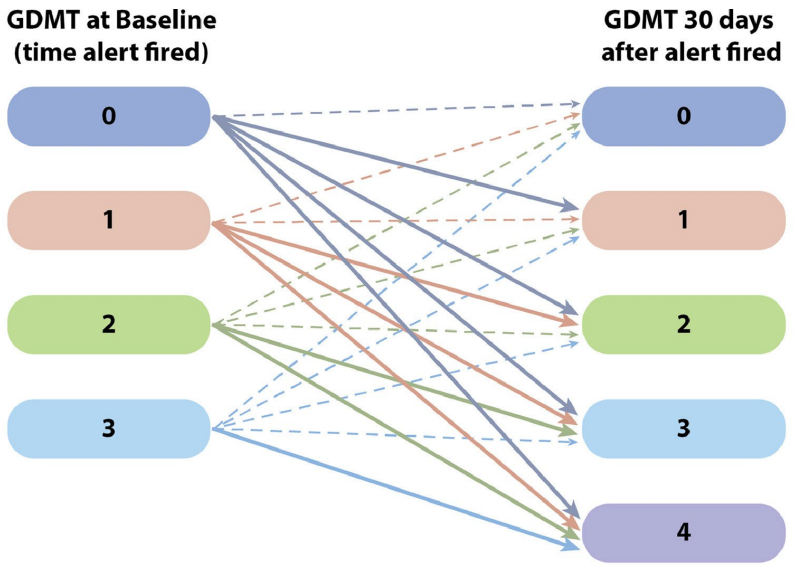
Alert Arm





Lama Ghazi et al. AHJ 2021; 9:409-419

Primary Outcome: Addition of GDMT Class



Scenario	Evidence-based medications at randomization	Evidence-based medications 30 days post-randomization	Outcome present (increase evidence-based medications)
1	ACEi + beta blocker	ARB + beta blocker	No
2	ARB + MRA	ARB + SGLT2i	No
3	ACEi	ACEi + SGLT2i + beta blocker	Yes
4	ACEi + MRA	ARNi	No
5	ARB + MRA + SGLT2i	ARB + MRA + SGLT2i + beta blocker	Yes
6	ACEi	ARNi	No

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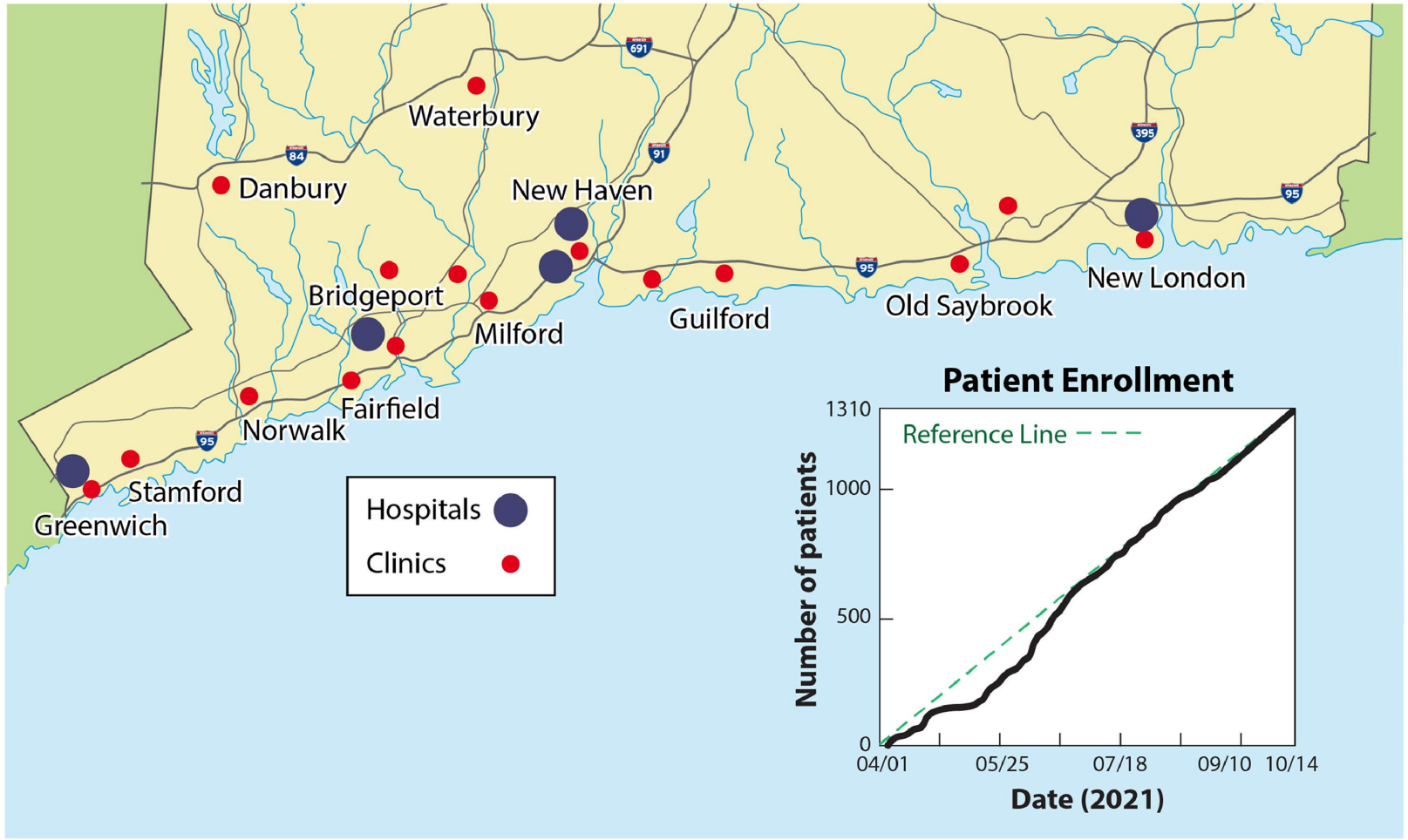
PROMPT-HF

Sample Size and Power Calculations

- Absolute increase of 10% in proportion of patients on an additional class of GDMT at 30 days
- Sample size of 1310 achieved 91% power to detect a 10% difference between study arms at $\alpha=0.05$ and ICC of 0.05
- Primary outcome examined association between intervention and outcomes using generalized linear models adjusting for prespecified baseline characteristics and accounting for clustering at provider level

Embedded EHR-Based Pragmatic Clinical Trial



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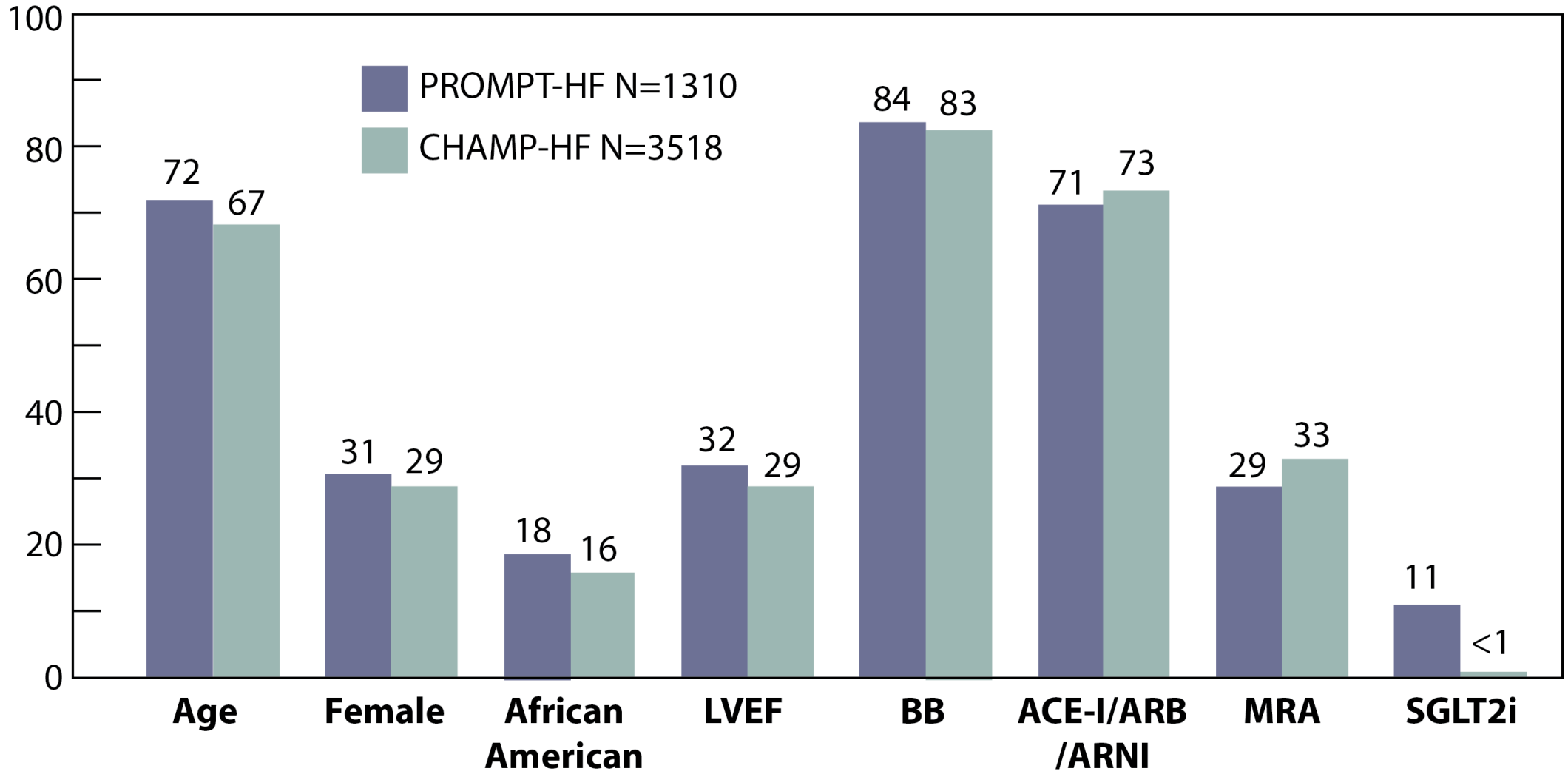
CTRA Clinical and Translational Research Accelerator

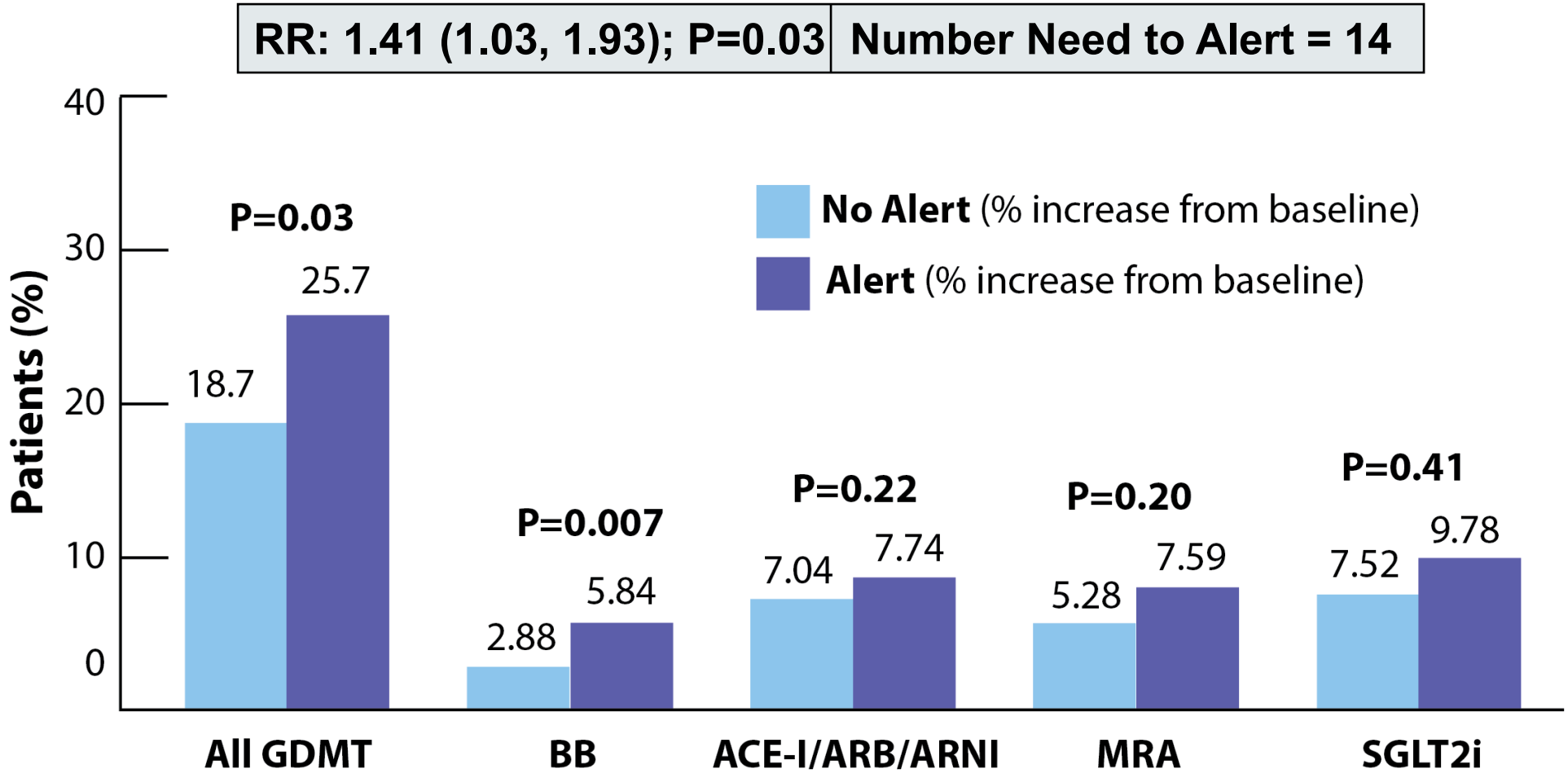
PROMPT-HF

Baseline Characteristics



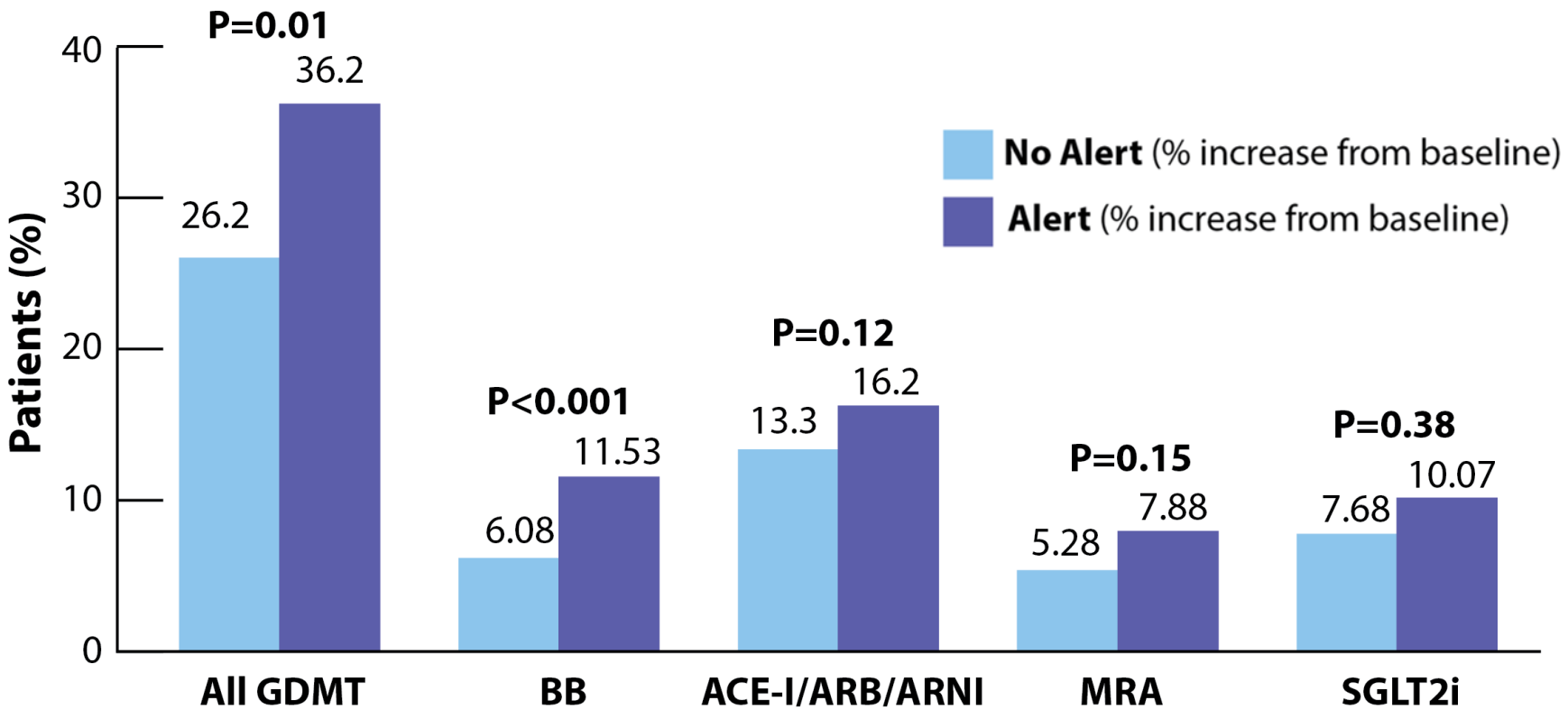
Stephen Greene et al. JACC 2018; 72(4):351-366.

Primary Clinical Endpoint: Additional GDMT Class



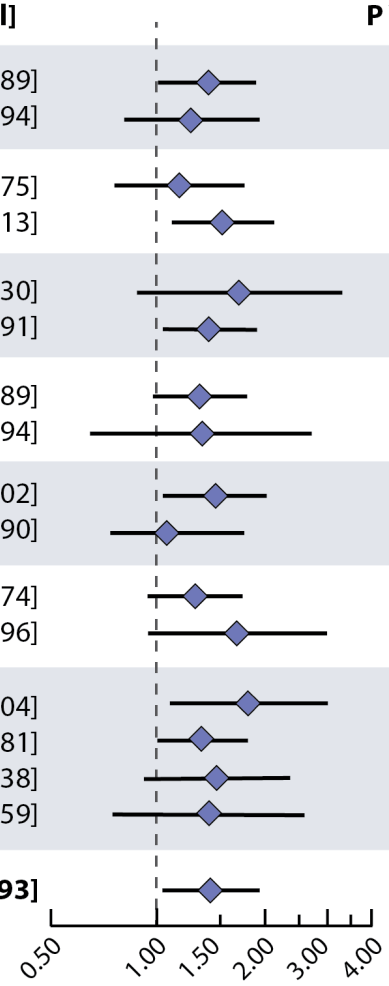
Secondary Clinical Endpoint: +GDMT Class/↑Dose

RR: 1.39 (1.08, 1.79); P=0.01 | **Number Need to Alert= 10**



Pre-Specified Subgroups

Subgroup	No. of Patients	RR [95%CI]	Interaction P Value
Age ≥ 65 yr	937	1.39 [1.01, 1.89]	0.86
Age < 65 yr	373	1.24 [0.79, 1.94]	
Female	402	1.15 [0.75, 1.75]	0.09
Male	908	1.53 [1.09, 2.13]	
Black	237	1.70 [0.87, 3.30]	0.67
Non-black	1073	1.40 [1.03, 1.91]	
LVEF ≥ 20%	1157	1.31 [1.01, 1.89]	0.41
LVEF < 20%	139	1.24 [0.79, 1.94]	
Cardiology	981	1.45 [1.04, 2.02]	0.65
Non-cardiology	329	1.05 [0.58, 1.90]	
Medicare/Medicaid	1117	1.27 [0.93, 1.74]	0.20
Other	193	1.57 [0.94, 2.96]	
GDMT: 0	80	1.81 [1.08, 3.04]	0.71
GDMT: 1	286	1.34 [0.99, 1.81]	
GDMT: 2	570	1.47 [0.91, 2.38]	
GDMT: 3	374	1.39 [0.75, 2.59]	
Overall	**1310**	**1.41 [1.03, 1.93]**	



Limitations

- Results from Single Health Care System
- Only Included High Volume Clinicians
- Tested in Outpatient Setting; Inpatient Trial Ongoing
- Tested within the Epic® EHR
- Increase in Dose was Secondary Outcome
- Impact Beyond 30 Days Subject of Future Study

Conclusions

A personalized alert triggered via the EHR during office visits led to significantly higher number of HFrEF patients on appropriate GDMT

This low-cost tool can be rapidly embedded into the EHR at integrated health care systems and lead to widespread improvements in the care of heart failure patients

Full Results Now Avalible Online

We Thank The Participants of PROMPT-HF

Questions or Comments
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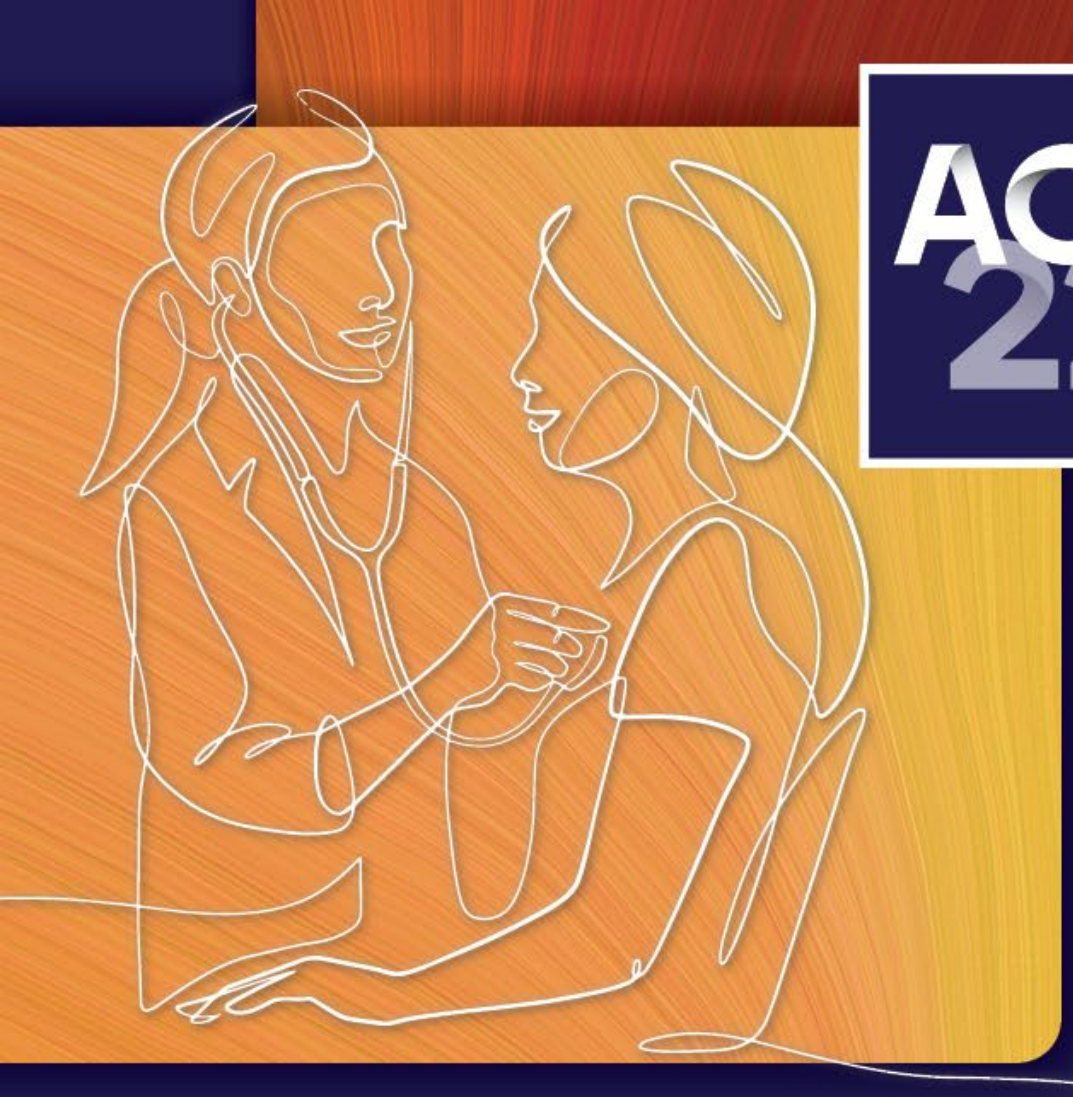
PROMPT-HF



ACC 22

A Randomized Trial to Confirm the Safety and Effectiveness of Chocolate Touch Paclitaxel Coated PTA Balloon Catheter in Above the Knee Lesions

Mehdi H. Shishehbor, DO, MPH, PhD on behalf of the Chocolate Touch Study Investigators

University Hospitals Harrington Heart and Vascular Institute, Cleveland, OH
@shishem

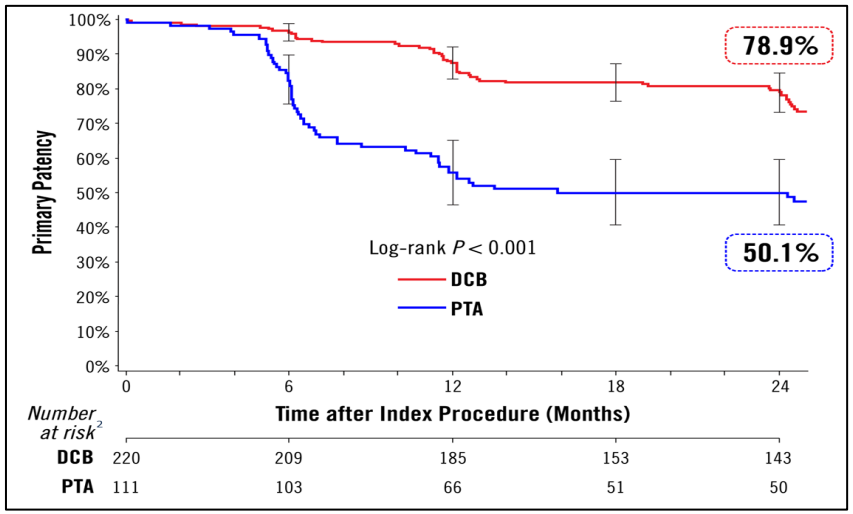
TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

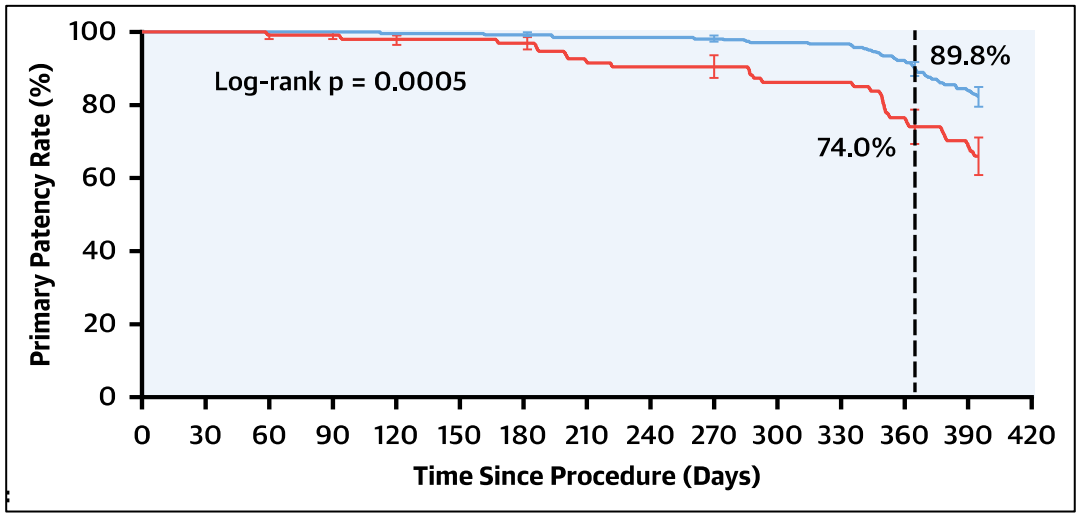
AMERICAN COLLEGE of CARDIOLOGY

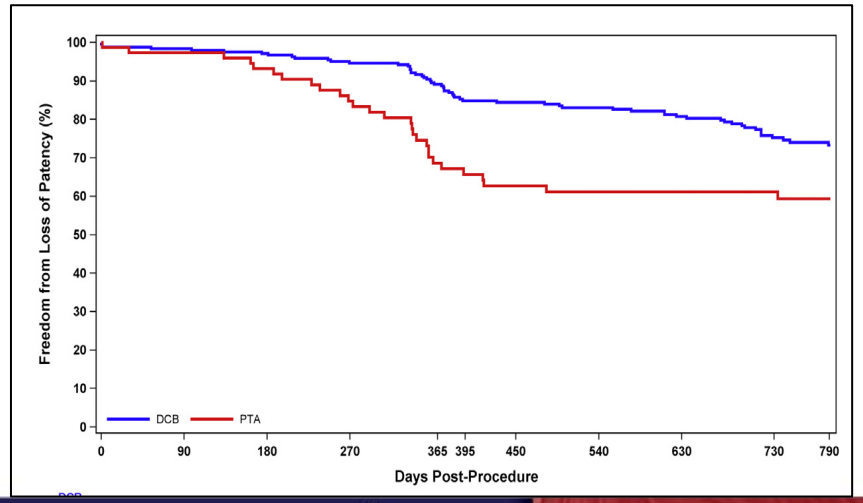
Disclosures

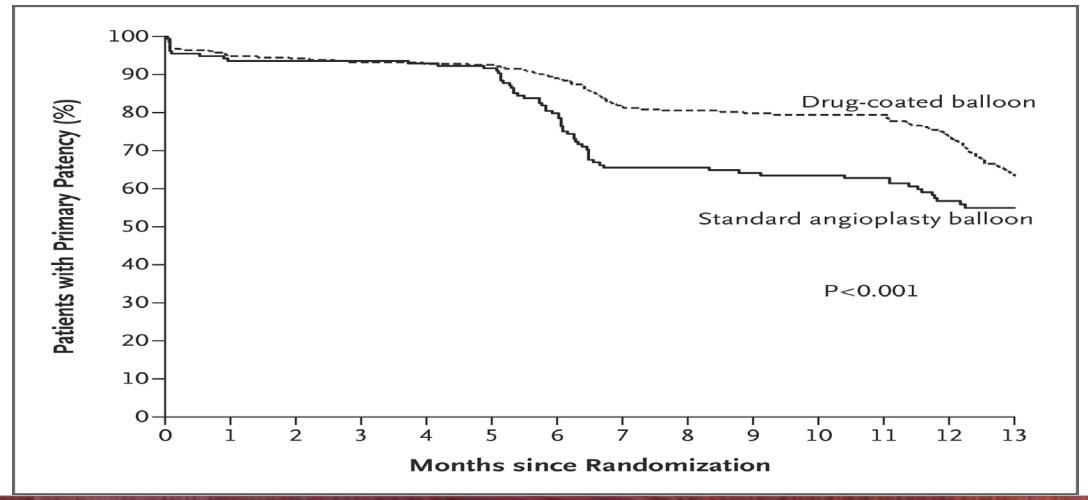
- Advisory board – Medtronic, Boston Scientific, Philips, Terumo, Abbott Vascular, ANT, Inquis Medical

Drug Coated Balloons Are Superior to Balloon Angioplasty





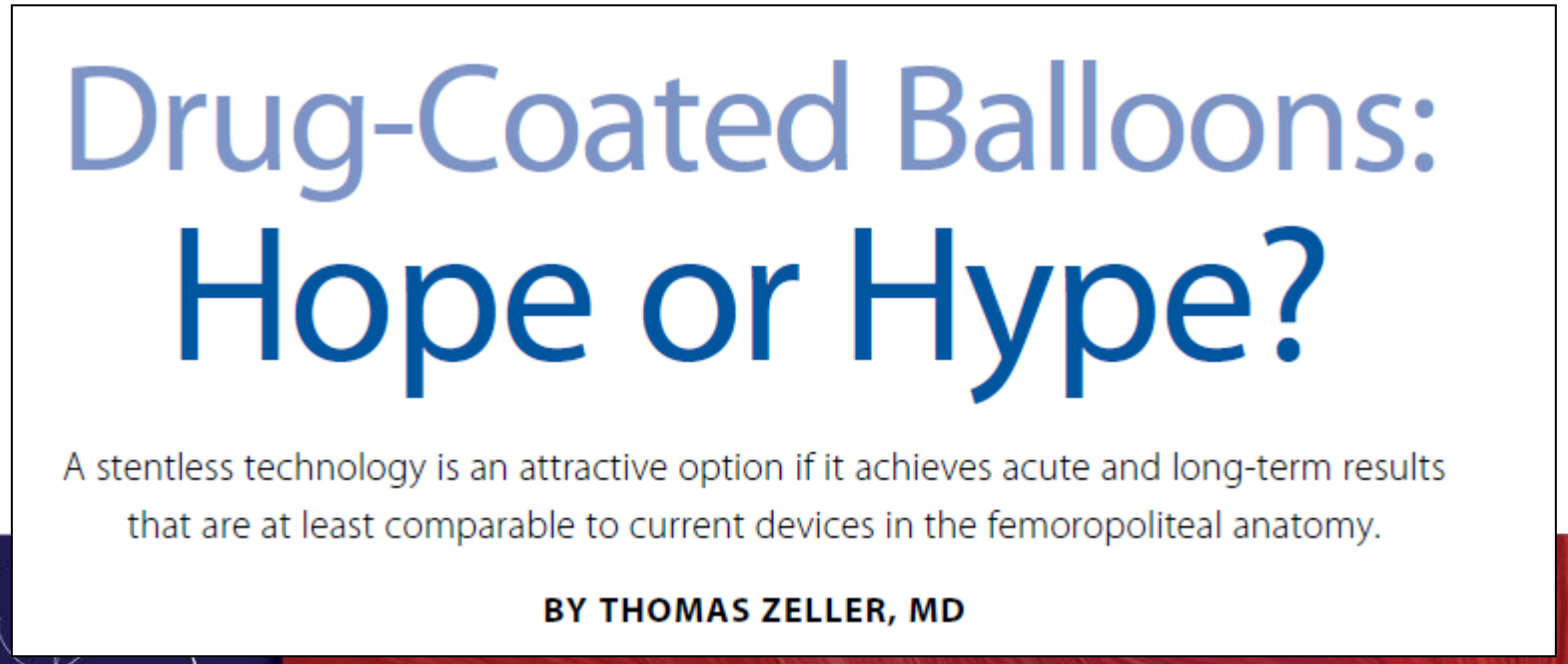




Krishnan et al. *Circulation*. 2017;136:1102-1113. Sachar et al. *JACC Cardiovasc Interv*. 2021;14:1123-1133. Rosenfield et al. *N Engl J Med*. 2015;373:145-53. Tepe et al. *Circulation*. 2015;131:495-502.

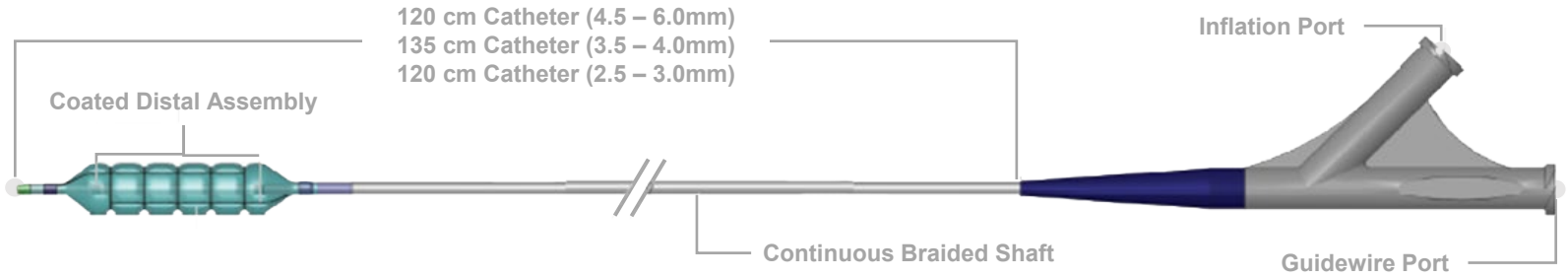
Current Limitations of Drug-Coated Balloons

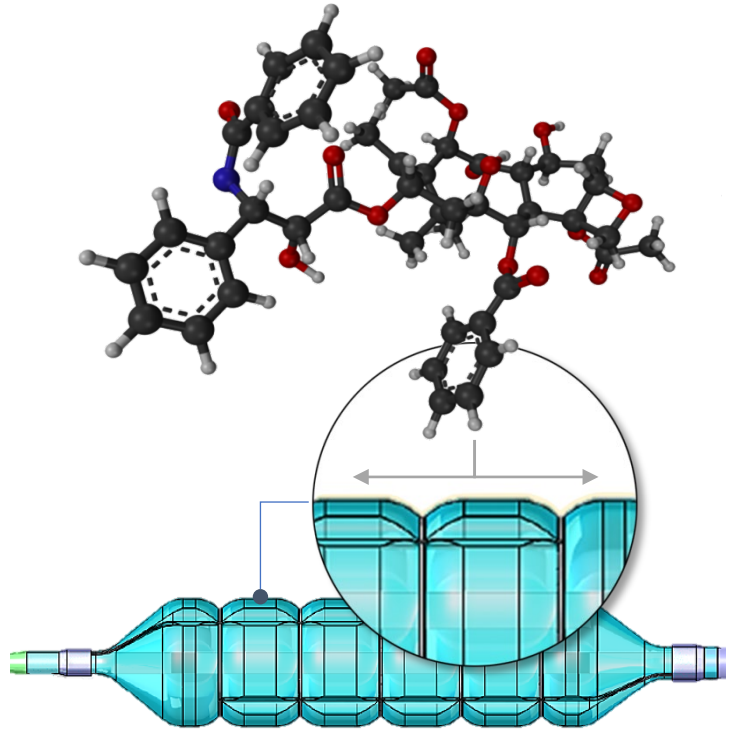
- Acute dissection and bailout stenting
- Significant recoil
- Minimal acute luminal gain
- Presence of Ca+



Purpose

- **Chocolate Touch DCB**
  - Pillow effect - nitinol constrained balloon designed to reduce vessel trauma and dissections
  - The distal assembly is coated with paclitaxel to inhibit neointimal formation





Chocolate Balloon Distal Assembly

- **Surface area increased by 20%**

- We sought to compare the efficacy and safety of the **Chocolate Touch DCB** to the commercially approved **Lutonix DCB** in an international randomized clinical trial

Chocolate Touch versus Lutonix DCB

	Chocolate Touch DCB	Lutonix DCB
Balloon	Chocolate™	Moxy™
Drug	Paclitaxel	Paclitaxel
Dose	3 μg/mm^2	2 μg/mm^2
Excipient	Propyl gallate	Polysorbate, Sorbitol
Sizing	1.1:1	1:1

Chocolate Touch Study Design

Open-label, randomized, non-inferiority trial
Patient with symptomatic SFA or popliteal arteries

34 sites (USA, Europe, New Zealand)
July 26, 2017, to May 26, 2020
1:1 Randomization

Chocolate Touch n=152

Lutonix n=161

20 Roll-in patients

30 d | **6 mo** | **12 mo** | **2 yr** | **3 yr** | **4 yr** | **5 yr**

Primary Endpoint: **Effectiveness** - True DCB success at **12 months**
Composite: Primary patency (peak systolic velocity ratio <2.4 without the need for clinically driven target lesion revascularization) in the absence of a clinically driven bail-out stenting (core lab adjudicated).

Primary Endpoint: **Safety** - Freedom from major adverse events (MAE) at **12 months**
Composite: Target limb-related death, major amputation of the target limb, or clinically driven reintervention of the target limb.

Statistical Design

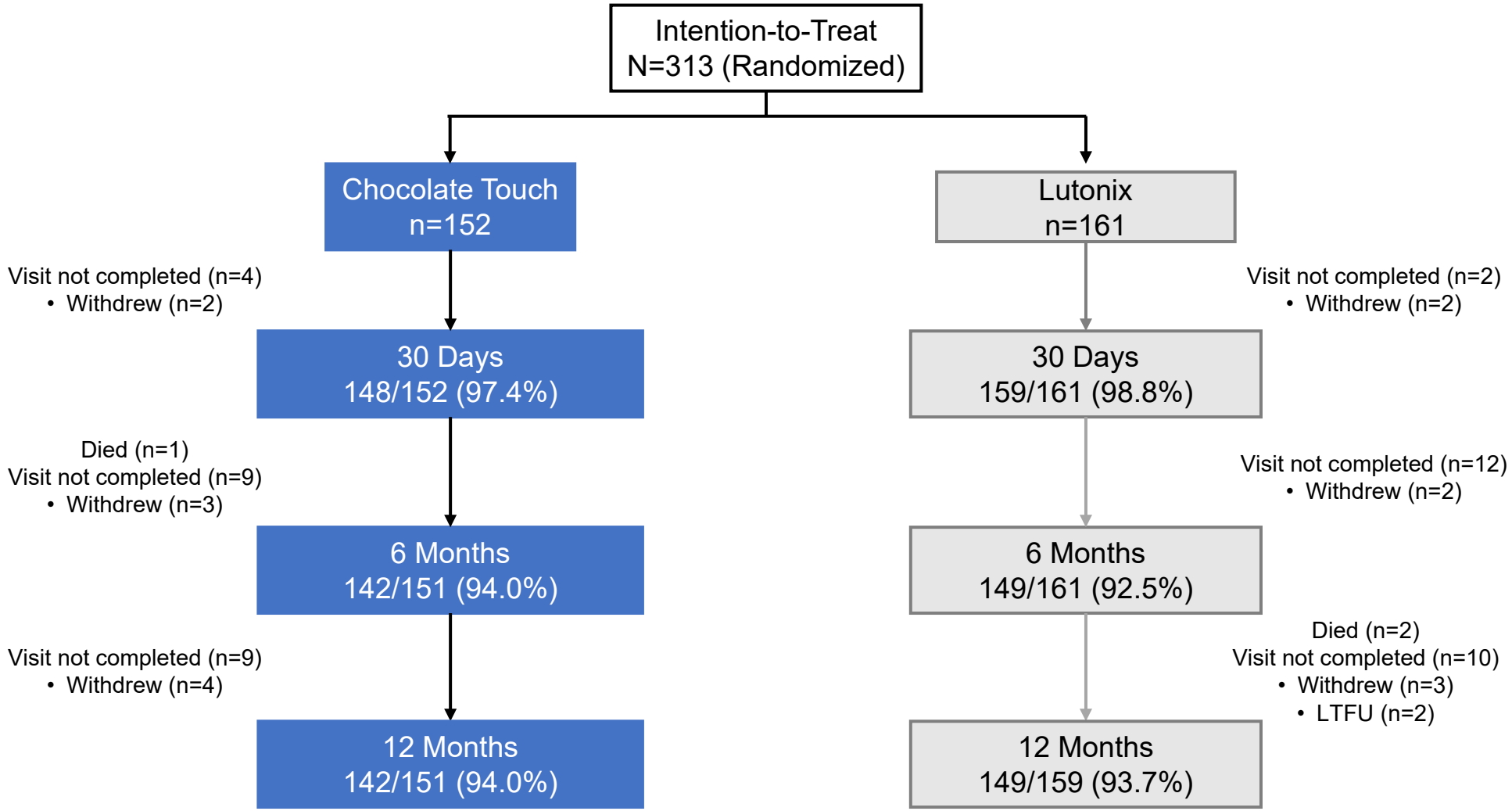
Primary Efficacy (DCB Success)	Primary Safety (Freedom from MAE)
Non-inferiority assumptions: 216 evaluable subjects would provide >90% power to declare non-inferiority • DCB success rate: 80% for Chocolate Touch and 70% for Lutonix • one-sided alpha=0.025 • 10% non-inferiority margin • 15% Loss to FU	**Non-inferiority** assumptions: 230 evaluable subjects would provide ~85% power to declare non-inferiority assuming • Freedom from MAE of 88% for Chocolate Touch and 84% in the Lutonix • one-sided alpha=0.025 • 10% non-inferiority margin
Sequential Superiority testing for Efficacy followed by Safety only if non-inferiority met for both primary endpoints tested at the two-sided alpha=0.05 level	
Trial Success required both primary efficacy and safety endpoints to meet non-inferiority	

This trial had an adaptive design with a prespecified interim analysis planned at 75% of enrolled patients with completed 12-month FU. Based on conditional power the trial allowed enrollment of a maximum population of 510 patients.

Trial Administration

Principal Investigators	**Mehdi Shishehbor, DO, MPH, PhD** **Thomas Zeller, MD, PhD**
Angiographic Core Lab **Clinical Events Committee** **Data Safety Monitoring Board**	**Yale Cardiovascular Research Group** Director: Alexandra J. Lansky, MD
Duplex Ultrasound Core Lab	**CoreLab Black Forest GmbH** Director: Ulrich Beschorner, MD

Study Flow and Follow-up



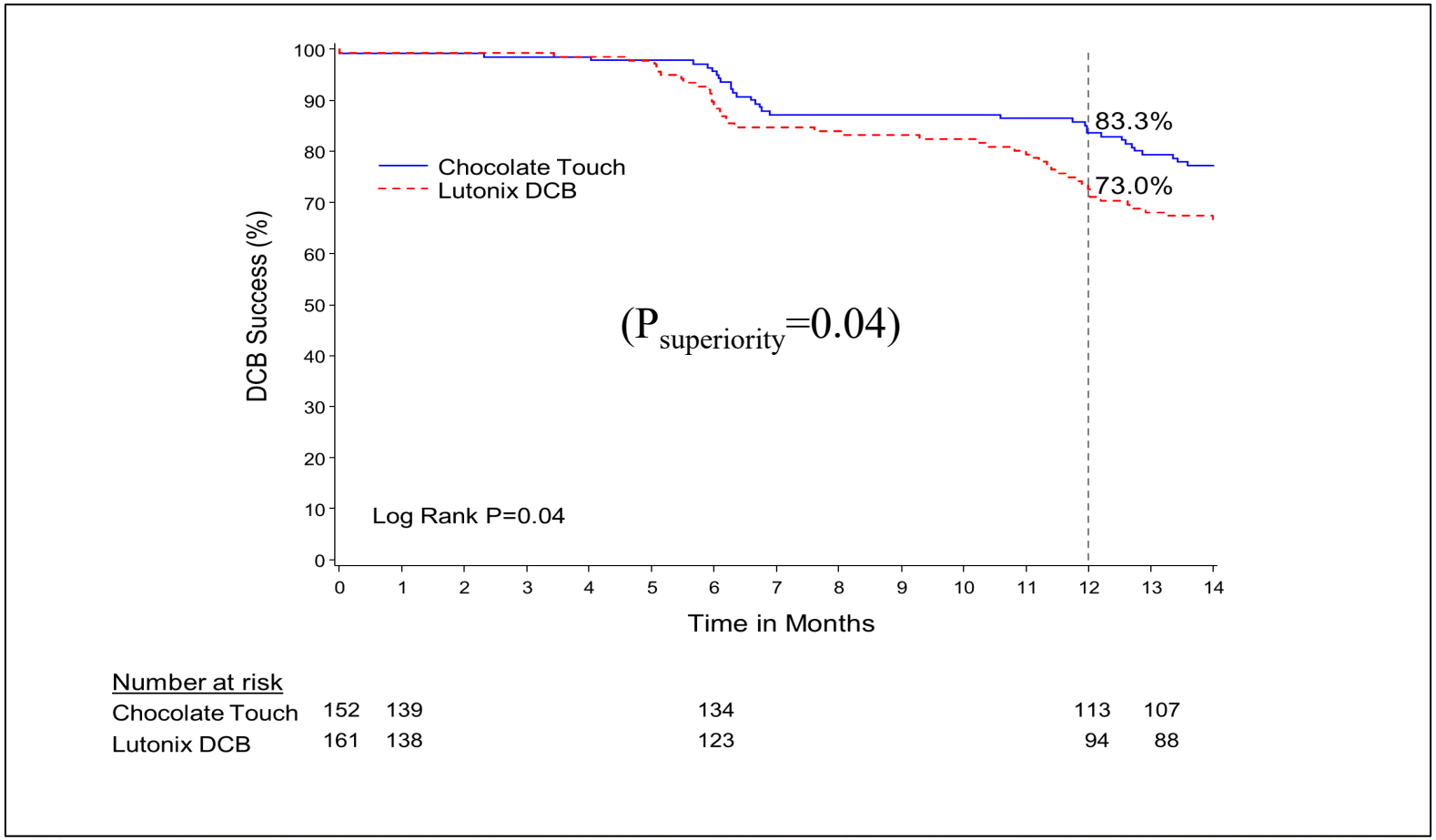
Baseline Characteristics

	Chocolate Touch	Lutonix DCB
Age	70.0±9.7	68.8±9.3
Male sex	57.2%	57.8%
Current smoker	33.6%	33.5%
Hypertension	90.1%	86.3%
Hyperlipidemia	86.2%	86.3%
Coronary artery disease	31.6%	46.6%
Chronic kidney disease	11.8%	8.1%
Diabetes mellitus	43.4%	32.9%
Rutherford category		
2	17.8%	14.4%
3	77.0%	80.0%
4	5.3%	5.6%
Ankle-brachial index	0.71±0.16	0.75±0.22

Angiographic and Procedural Characteristics

	Chocolate Touch	Lutonix DCB
Lesion Length, mm	78.5 ± 46.3	77.8 ± 47.7
Total occlusion, %	22.0	20.3
Severe Calcification, %	25.0	21.3
Atherectomy device use, %	12.5	11.2
Dissection requiring bailout stenting, %	0	0
Flow limiting dissection, %	0	0

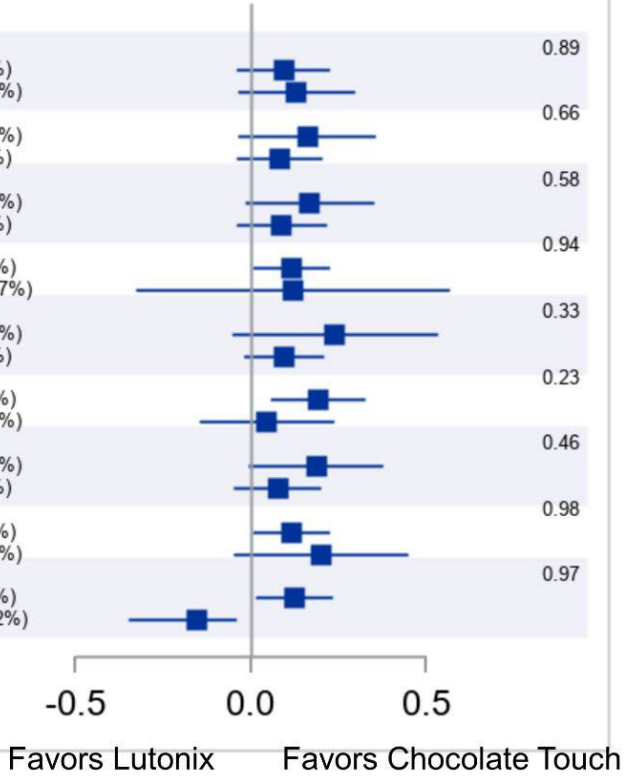
Primary Efficacy Endpoint (Chocolate Touch 78.8% versus Lutonix DCB 67.7%) ($P_{non\text{-}inferiority}<0.0001$)



Chocolate Touch DCB Showed Consistent Efficacy

Primary Effectiveness Endpoint of True DCB Success at 12 Months

Subgroup	Chocolate Touch	Lutonix	Difference (95% CI)	Interaction P-Value
Sex				0.89
Male	66/81 (81.5%)	52/72 (72.2%)	9.3% (-4.1%, 22.6%)	
Female	42/56 (75.0%)	36/58 (62.1%)	12.9% (-3.9%, 29.8%)	
Geography (US VS OUS)				0.66
US	31/42 (73.8%)	26/45 (57.8%)	16.0% (-3.6%, 35.7%)	
OUS	77/95 (81.1%)	62/85 (72.9%)	8.1% (-4.2%, 20.4%)	
Diabetes				0.58
Diabetes	44/57 (77.2%)	26/43 (60.5%)	16.7% (-1.5%, 35.0%)	
No Diabetes	64/80 (80.0%)	62/87 (71.3%)	8.7% (-4.2%, 21.7%)	
Baseline Rutherford				0.94
<=3	103/131 (78.6%)	82/122 (67.2%)	11.4% (0.5%, 22.3%)	
>3	5/6 (83.3%)	5/7 (71.4%)	11.9% (-32.9%, 56.7%)	
Predilatation				0.33
Atherectomy	15/17 (88.2%)	9/14 (64.3%)	23.9% (-5.5%, 53.4%)	
Standard Balloon Angioplasty	93/120 (77.5%)	79/116 (68.1%)	9.4% (-1.9%, 20.7%)	
Calcification				0.23
Minimal/None	68/84 (81.0%)	50/81 (61.7%)	19.2% (5.7%, 32.7%)	
Moderate/Severe	34/45 (75.6%)	27/38 (71.1%)	4.5% (-14.6%, 23.6%)	
Lesion Length				0.46
<=10	36/47 (76.6%)	25/43 (58.1%)	18.5% (-0.6%, 37.5%)	
>10	72/90 (80.0%)	63/87 (72.4%)	7.6% (-4.9%, 20.1%)	
Treatment Location				0.98
Hospital Based Procedure	103/132 (78.0%)	80/120 (66.7%)	11.4% (0.4%, 22.4%)	
Outpatient Based Lab	5/5 (100.0%)	8/10 (80.0%)	20.0% (-4.8%, 44.8%)	
Location				0.97
SFA	97/124 (78.2%)	81/123 (65.9%)	12.4% (1.3%, 23.5%)	
Popliteal	11/13 (84.6%)	7/7 (100.0%)	-15.4% (-35.0%, 4.2%)	



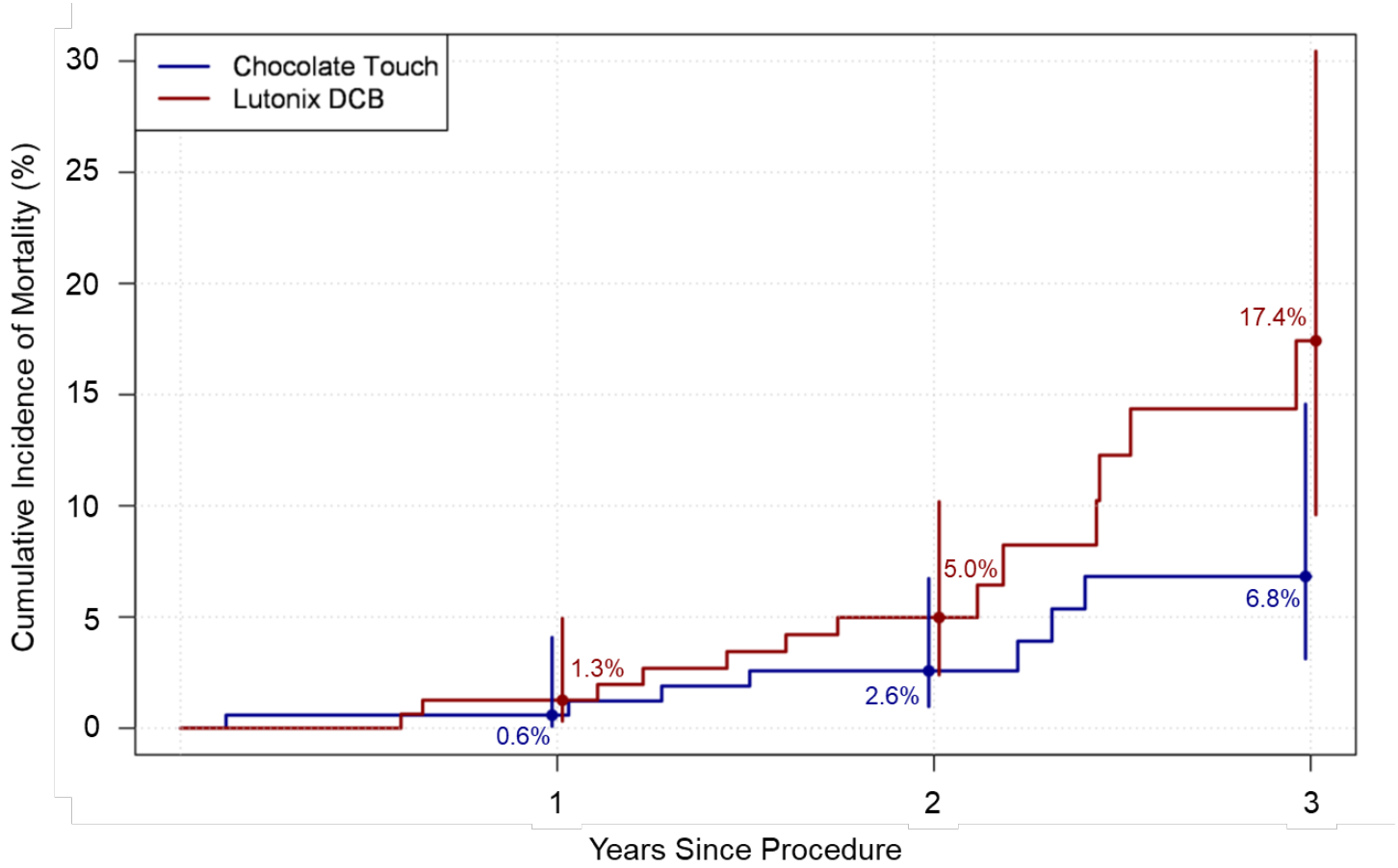
Interaction P-value from the fixed effects logistic regression model treatment by subgroup interaction term.

Chocolate Touch Met Its Primary Safety Endpoint

Event	Chocolate Touch	Lutonix DCB	Difference (95% CI)	Non-inferiority P-Value	Superiority P-value
Freedom from MAE	88.9%	84.6%	4.3% (-3.4%, 12.1%)	0.0001	0.2759
Target Limb-Related Death	0.7%	0.0%	0.7% (-0.7%, 2.1%)		
Major Target Limb Amputation	0.0%	0.0%	—		
Target Limb re-Intervention	10.5%	15.4%	-4.9% (-12.6%, 2.7%)		

Primary Safety endpoint met non-inferiority

Similar Mortality Was Observed in the As Treated Population



Number at Risk				
Chocolate Touch	171	159	119	44
Lutonix DCB	160	154	106	22

Conclusions

- The Chocolate Touch Study met its primary effectiveness endpoint of **True DCB Success** at 12 months:
  - Non-inferiority
  - Superior efficacy
- Chocolate Touch also met its non-inferiority endpoint for safety
- No difference in mortality, although the trial was not adequately powered for a mortality endpoint

Thank You!

It's time to change the math.

ACC 22

Global Heart Attack Treatment Initiative

Quality Improvement for STEMI Care

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

Improving STEMI Management Internationally: Two-year Report of 4,015 Patients Enrolled in the American College of Cardiology Global Heart Attack Treatment Initiative

Cesar J. Herrera, Benny J. Levenson, Ana C. Lucca, Angela Natcheva, Kyoko Miki, Kelly Olsson, Alyssa McCormick, B. Hadley Wilson, and the GHATI Investigators

Global Heart Attack Treatment Initiative (GHATI)
American College of Cardiology, Washington, DC

Disclosures

The following authors have nothing to disclose:

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★ **Initial cohort (Q4 2019)**

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★ **Initial cohort (Q4 2019)**

Background

- Over 3 million STEMIs are estimated to occur annually in low- and middle-income countries.
- Little data exist on system-based initiatives and measurement of performance metrics of STEMI in these nations.
- GHATI encourages adherence to Guidelines and tracking of clinical and institutional indicators.

Goals

- Collect data across the care continuum to evaluate and improve evidence-based STEMI management.
- Use data/QI efforts to enact change within health systems.
- Promote consistent application of optimal, Guideline-directed treatments for STEMI.
- Encourage adherence to evidence-based secondary prevention regimens, including medication use.

Q4 2021 Participants

Participants	Sites	Countries
Initial cohort	9	7
Q1 2020	15	11
Q2-Q4 2020	18	13
Q1-Q2 2021	20	14
Q3 2021	22	15
Q4 2021	39	18

Initial cohort: Mexico, Dominican Republic, Argentina, Saudi Arabia, Pakistan, Bangladesh, Malaysia

Q1 2020: + Brazil, India, Kenya, UAE

Q2-Q4 2020: + North Macedonia, Singapore

Q1-Q2 2021: + Cuba

Q3 2021: + Paraguay

Q4 2021: + Costa Rica, Egypt, Peru

GHATI
GLOBAL HEART ATTACK TREATMENT INITIATIVE

Methods

- Data elements derived from the ACC Chest Pain-MI Registry collected prospectively, aggregated, and reported quarterly by Hospital between October 1, 2019 – September 30, 2021.
- No direct patient health information included in submissions; Hospital identifiers anonymized.
- Adherence to Guidelines by Hospital was measured for the initial cohort at two-years, using a rolling 4-quarters quantified using significance tests (t-Test and Wilcoxon).

ACC Chest Pain-MI Performance Metrics and Data Points

Elements	Description
E1	Reason for delay at facility
E2	Transportation time
E3	Mean and Median time: First Medical Contact (FMC) to Electrocardiogram (ECG)
E4	Mean and Median time: Arrival to Electrocardiogram (ECG)
E5	Mean and Median time: Arrival to Cath Lab
E6	Mean and Median time: Arrival to Fibrinolytic Therapy
E7	Mean and Median time: Arrival to Device Time
E8	Proportion of Patients with LVEF <40%
E9	Proportion of Patients Discharged Alive
E11	Proportion of Patients receiving P2Y12 inhibitor between First Medical Contact (FMC) and Catheterization
E12	Proportion of Patients Received at facility in Cardiogenic Shock
E13	Patients who experienced cardiac arrest before intervention
E14	Patients who experienced cardiac arrest after intervention
E15	Patients who are current smokers
E16	Patients who are female (sex)

Performance Metrics	Description
PM1	Aspirin upon arrival
PM2	Aspirin prescribed at discharge
PM3	Beta-blocker at discharge
PM4	Statin at discharge
PM5	Evaluation of LVEF
PM6	ACE-I or ARB for LVSD (<40% LVEF) at discharge
PM7	Door-to-Needle Time (fibrinolytic therapy)
PM8	STEMI patients receiving primary PCI within 90 minutes
PM9	Reperfusion therapy
PM13	P2Y12 inhibitor at discharge

GHATI
GLOBAL HEART ATTACK TREATMENT INITIATIVE

Results (1)

To date, 4,212 consecutive patients with STEMIs have been enrolled,

4,015 are reported here:

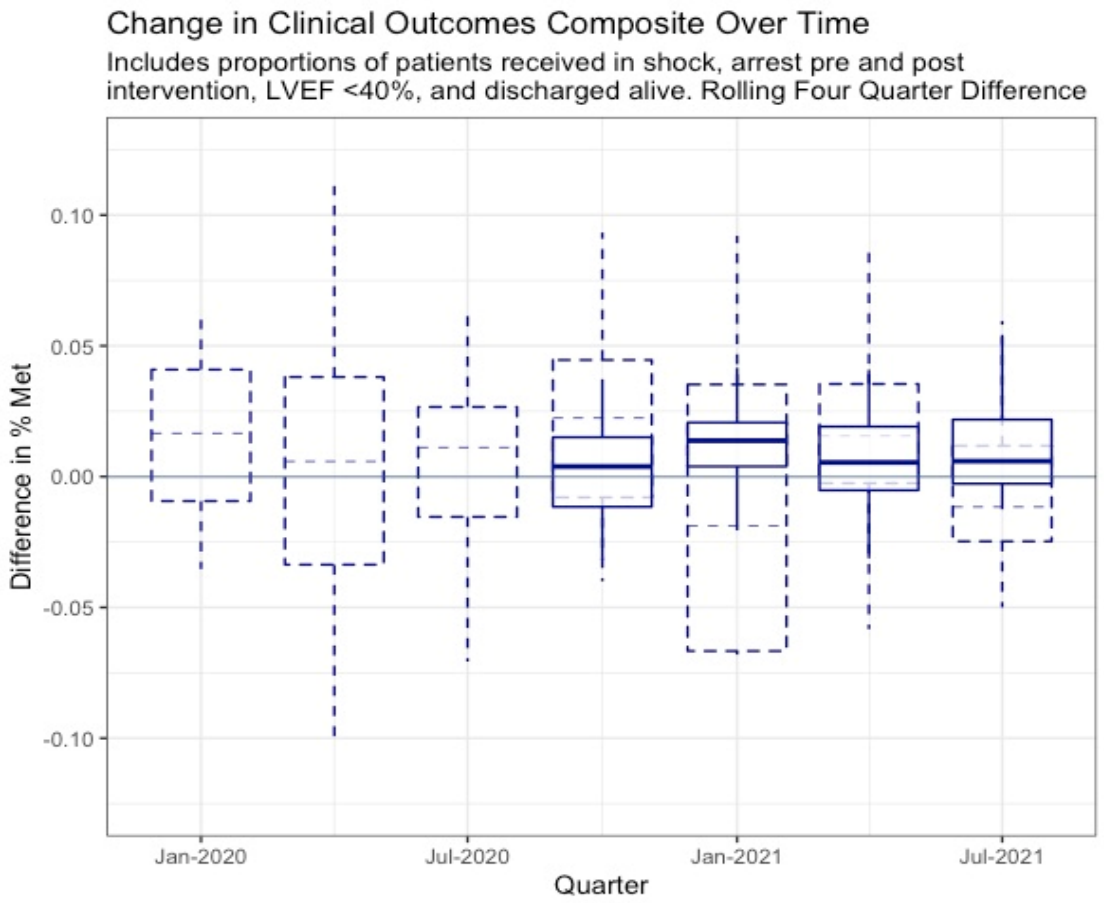
- Female – **mean 19.5% (IQR – 10.5%)**
- Smokers – **35.5% (15.3%)**
- Cardiogenic shock on arrival – **10% (7.3%)**
- Cardiac arrest before intervention – **5.1% (4.4%)**

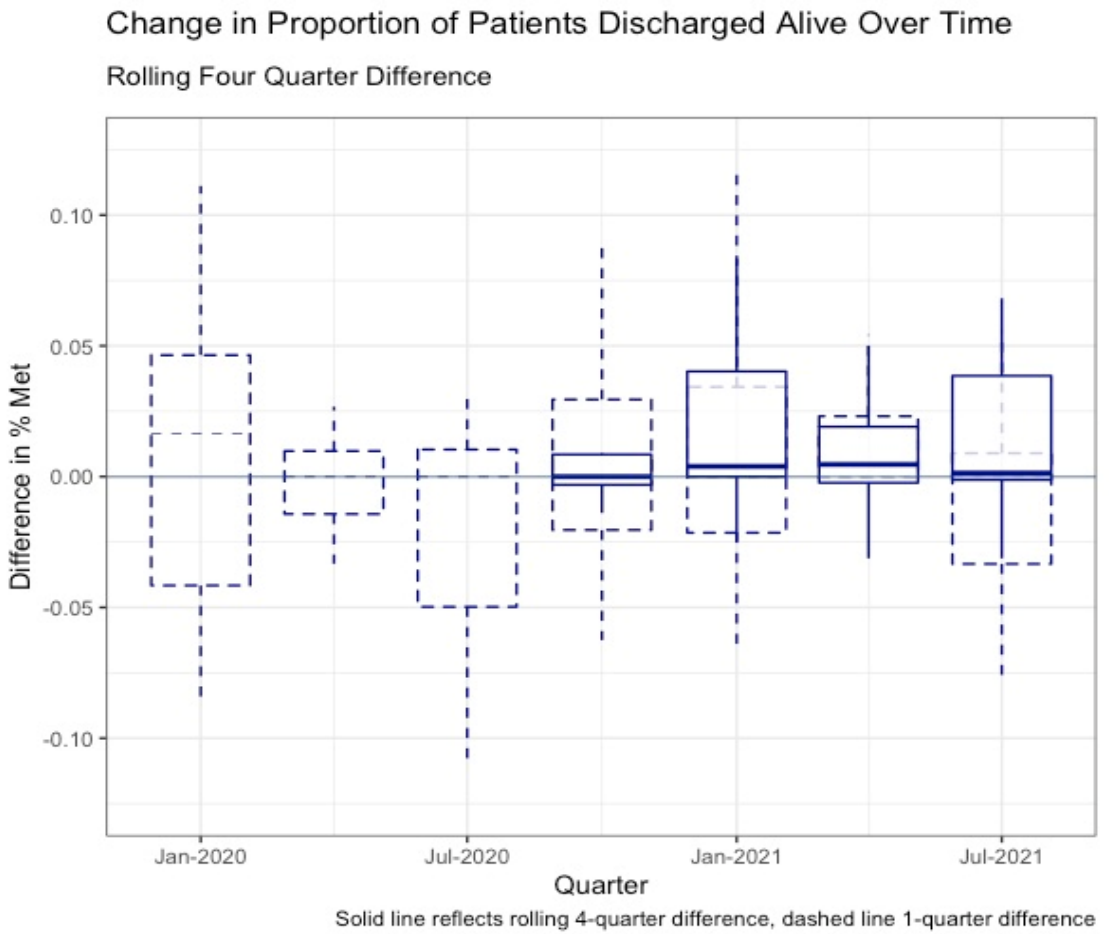
Results (2)

- We observed improvement in combined endpoints of shock on arrival, arrest before / after intervention, final EF < 40%, and survival at discharge: **1st to last Quarter mean difference of 3.1% (IQR 4.3%)**.

- Improvement in proportion of patients discharged alive over time was also noted: **mean difference 1.7% (IQR 3.5%)**.

Results (3)


Change in Clinical Outcomes Composite Over Time
Includes proportions of patients received in shock, arrest pre and post intervention, LVEF <40%, and discharged alive. Rolling Four Quarter Difference
Difference in % Met
0.10
0.05
0.00
-0.05
-0.10
Jan-2020
Jul-2020
Jan-2021
Jul-2021
Quarter


Change in Proportion of Patients Discharged Alive Over Time
Rolling Four Quarter Difference
Difference in % Met
0.10
0.05
0.00
-0.05
-0.10
Jan-2020
Jul-2020
Jan-2021
Jul-2021
Quarter
Solid line reflects rolling 4-quarter difference, dashed line 1-quarter difference

Results (4)

Additional findings included sustained high rates of:

- First Medical Contact – Device Time < 90 min: **mean 70%+**
- Reperfusion therapy: **mean 90%+**
- Evaluation of LVEF: **mean 85%+**
- Use of Guideline-Directed Medical Therapy: **mean 85%+**

Limitations

- Not all-comers registry.
- Relatively small initial cohort.
- Scant system-based quality assessment experience.
- Limited availability of electronic health records.
- Restricted by the use of aggregated data, not patient health information.

Conclusions

- This global contemporary registry successfully enrolled STEMI patients in countries generally unfamiliar with Quality Improvement metrics.
- Important trends of clinical parameters improvement were observed.
- GHATI may facilitate the implementation of policies aimed at enhancing outcomes of CV disease worldwide.

Future of GHATI

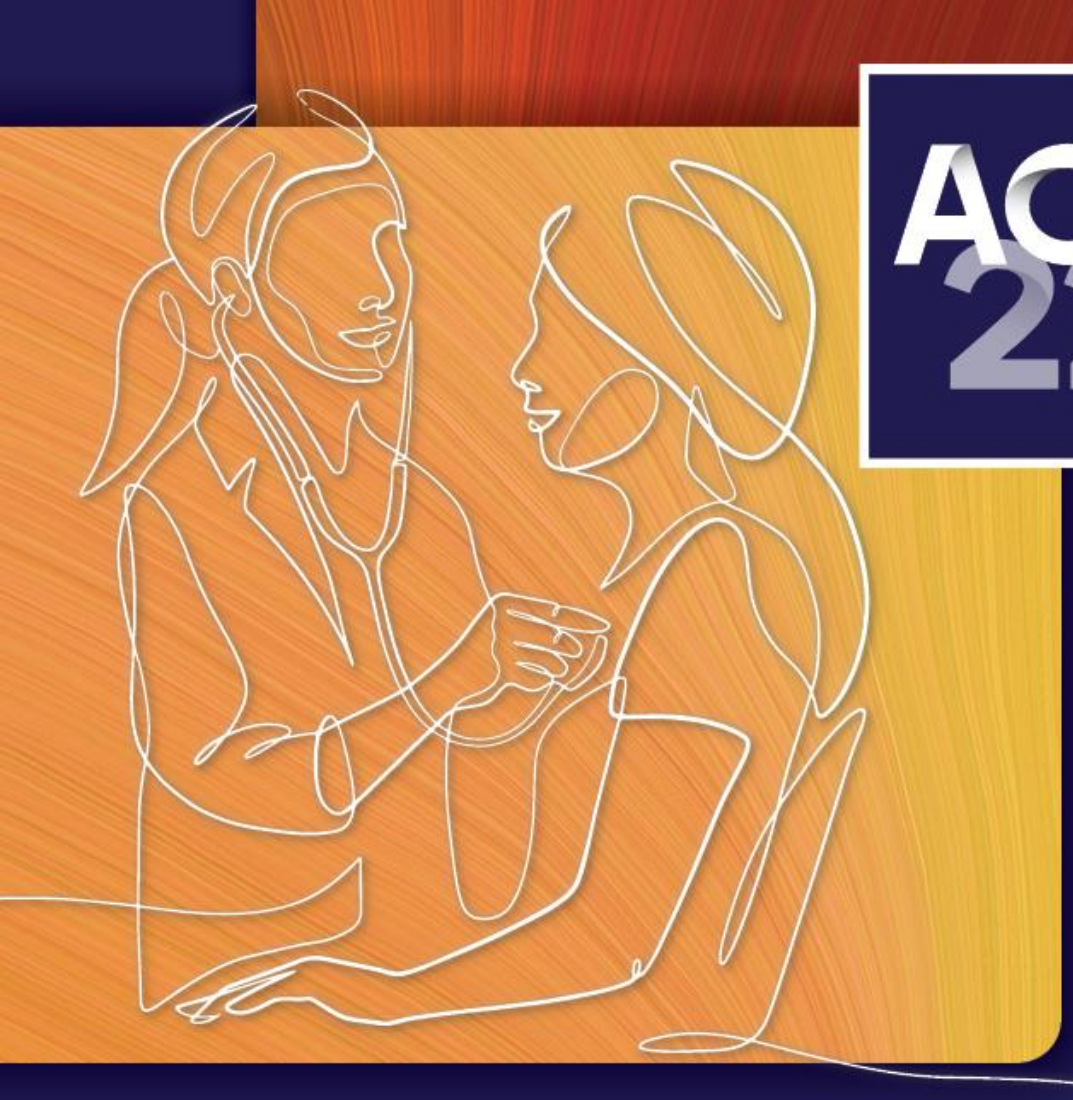
- Establish long-term, worldwide STEMI systems of care.
- Continue and expand global rollout.
- Address culture change locally.
- Study potential gender / regional differences on STEMI care.
- Collaboration with other Quality Assessment programs.

Join GHATI!

www.acc.org/ghati
ghati@acc.org

ACC's Global Heart Attack Treatment Initiative

A Global Opportunity - We look forward to collaborating with you to advance STEMI care around the world.



ACC 22

Late Breaking Clinical Trial - 4 April 2022

Sodium Thiosulfate in Myocardial Infarction (GIPS-IV)

Marie-Sophie L.Y. de Koning, Paulien van Dorp, Solmaz Assa, Michiel Voskuil, Rutger L. Anthonio, D. Veen, Tim Leiner, Anita J. Sibeijn-Kuiper, Harry van Goor, Dirk J. van Veldhuisen, Peter van der Meer, Robin Nijveldt, Erik Lipšic, Pim van der Harst, and the GIPS-IV investigators

University Medical Center Groningen
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#GIPSIV
@profpim
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AMERICAN COLLEGE of CARDIOLOGY

Disclosures and funding

- M.L.Y. de Koning has no conflicts of interest
- Discusses off-label and investigational use of sodium thiosulfate
- Funded by:

ZonMw
Hartstichting
SIEMENS Healthineers
umcg

Background

Myocardial infarction still major risk factor for heart failure development and early mortality

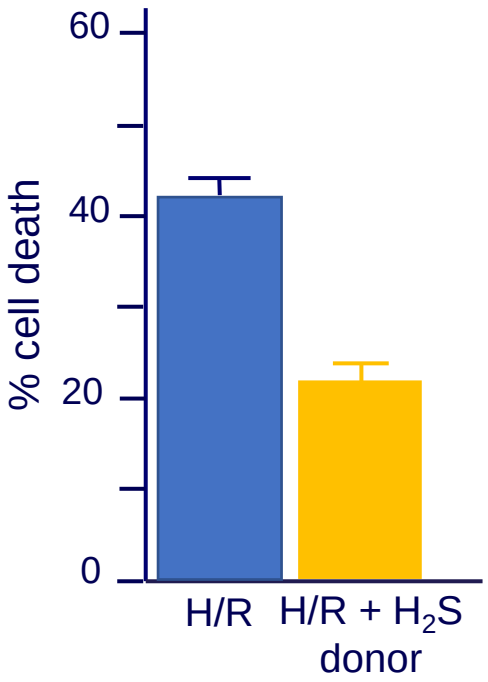
- Infarct size: strongest predictor of clinical outcomes

Residual target to limit infarct size: ischemia-reperfusion injury

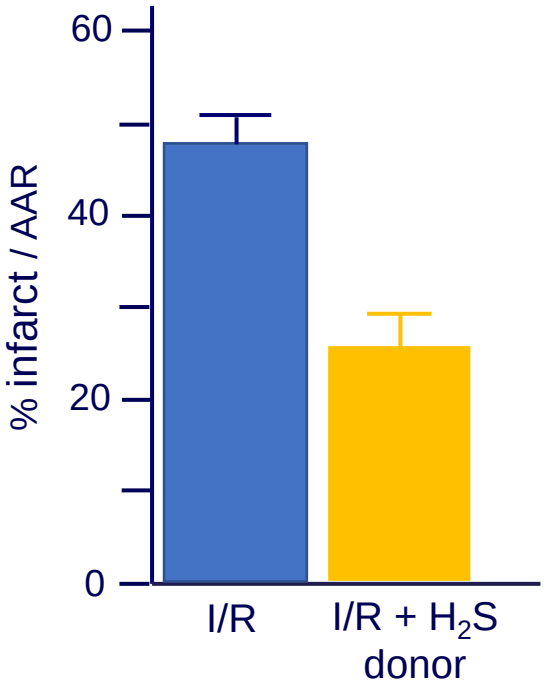
Hydrogen Sulfide (H_2S) very promising cardioprotective therapy

Pre-clinical evidence

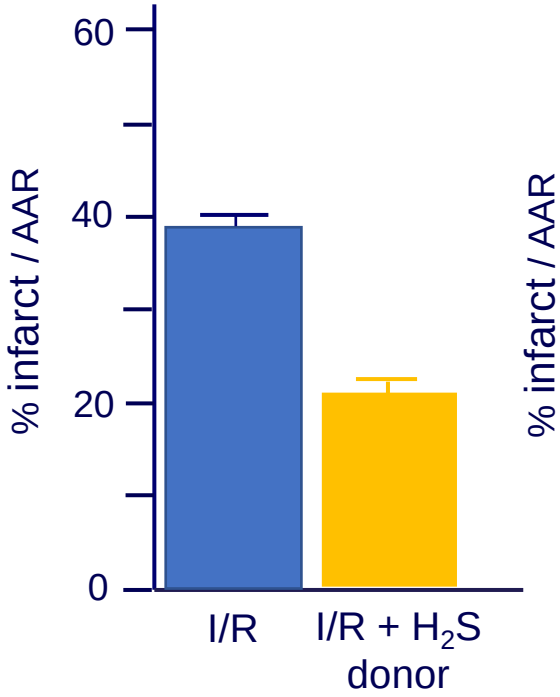
Myocardial I/R



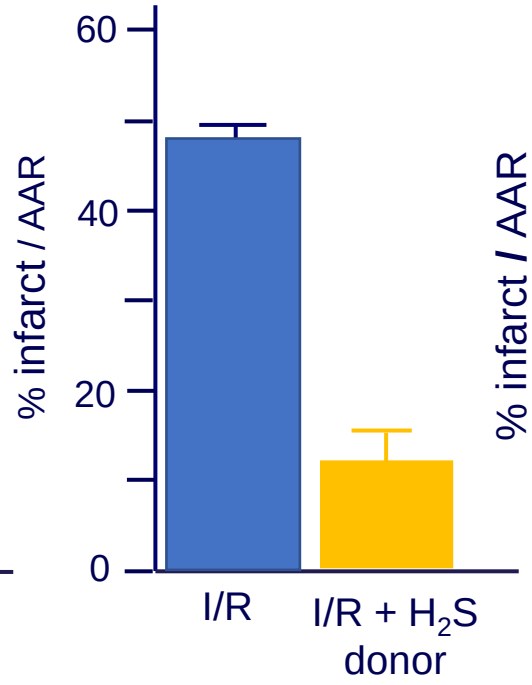
cellular[1] cardiomyocytes



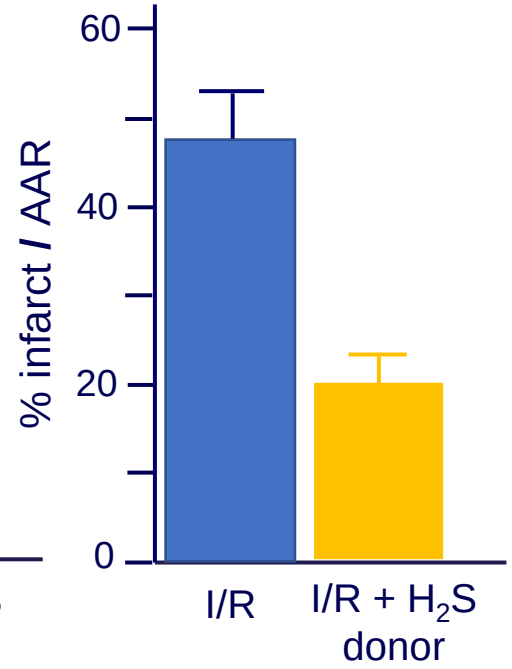
mouse[2]



rat[3]



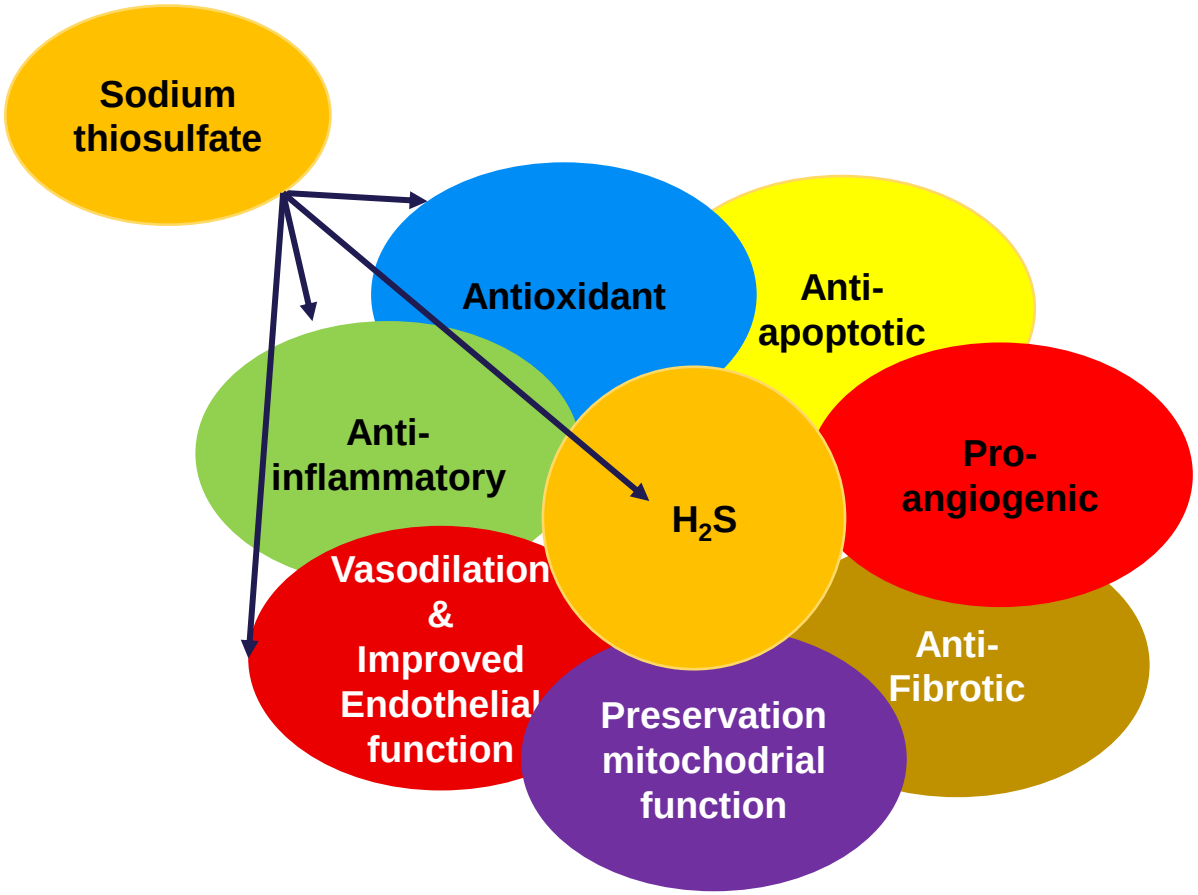
rabbit[4]



swine[5]

1. Kannan et al. *Cell Biochemistry and* Biophysics *2019*
2. Calvert et al. *Circ Res 2009*
3. Ravindran et al. *J. Cardiovasc Transl Res 2018*
4. Bibli et al. *Cardiovasc Res 2015*
5. Sodha et al. *Eur J. Cardiothoracic surgery 2008*

Mechanisms and safety profile



Clinical safety

- Cyanide poisoning
- Cisplatin-related ototoxicity[1,2] (children)
- Calciphylaxis[3]
- Pilot study, acute coronary syndrome[4]

1. Brock et al. *NEJM 2018*
2. Freyer et al. *Lancet Oncol 2017*
3. Peng et al. *Nephrology 2017*
4. De Koning et al. *J. Interv Cardiol 2020*

Groningen Intervention Study for the Preservation of cardiac function with Sodium thiosulfate after ST-segment elevation myocardial infarction (GIPS-IV)

Proof-of-principle trial

Randomized, double-blind, placebo-controlled, multicenter, phase 2 trial

Objective: to investigate whether sodium thiosulfate (STS) at reperfusion reduces infarct size in patients presenting with a first STEMI

NCT 02899364

Eligibility criteria

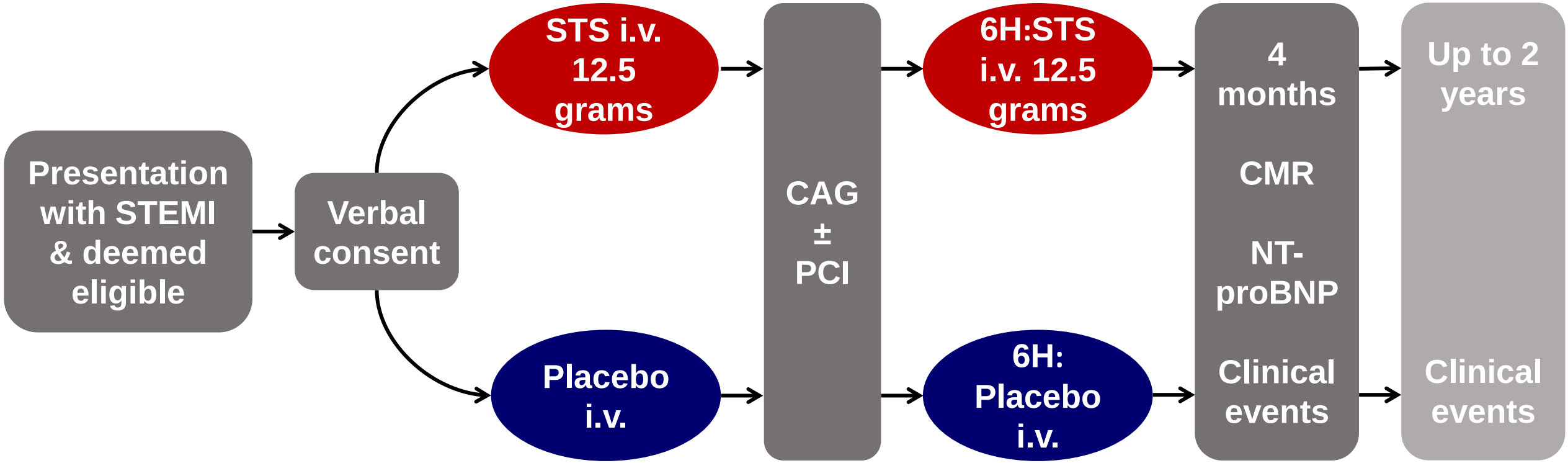
Key inclusion criteria

- Presentation with STEMI
- Age ≥ 18 years
- Ongoing ST-segment deviation and/or symptoms
- Onset complaints <12 hours before arrival at Cath Lab

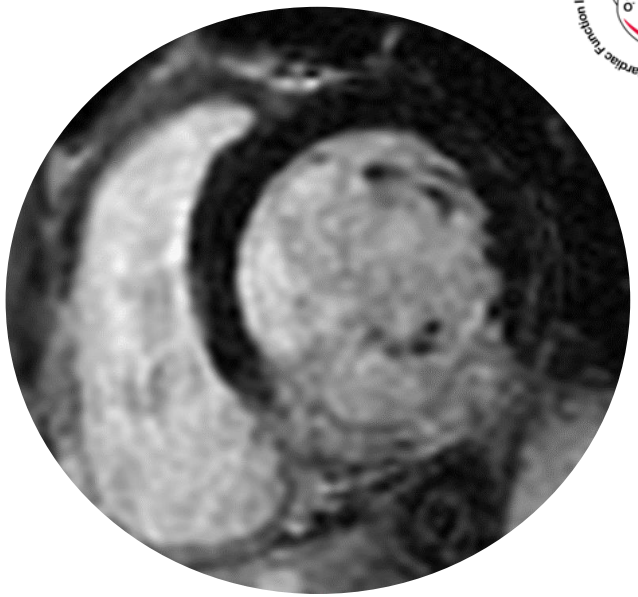
Key exclusion criteria

- Prior myocardial infarction, CABG, cardiomyopathy
- Conditions that would obscure CMR

Trial design and intervention



Study outcomes



Primary outcome

- Infarct size (% of left ventricle), measured by CMR after 4 months

Secondary outcomes

- Peak Creatine-Kinase MB during index hospitalization
- LVEF at CMR after 4 months
- NT-proBNP levels after 4 months
- Safety endpoints, including MACE, up to 4 months

Sample size determination

Hypothesis: STS reduces infarct size

Sample size

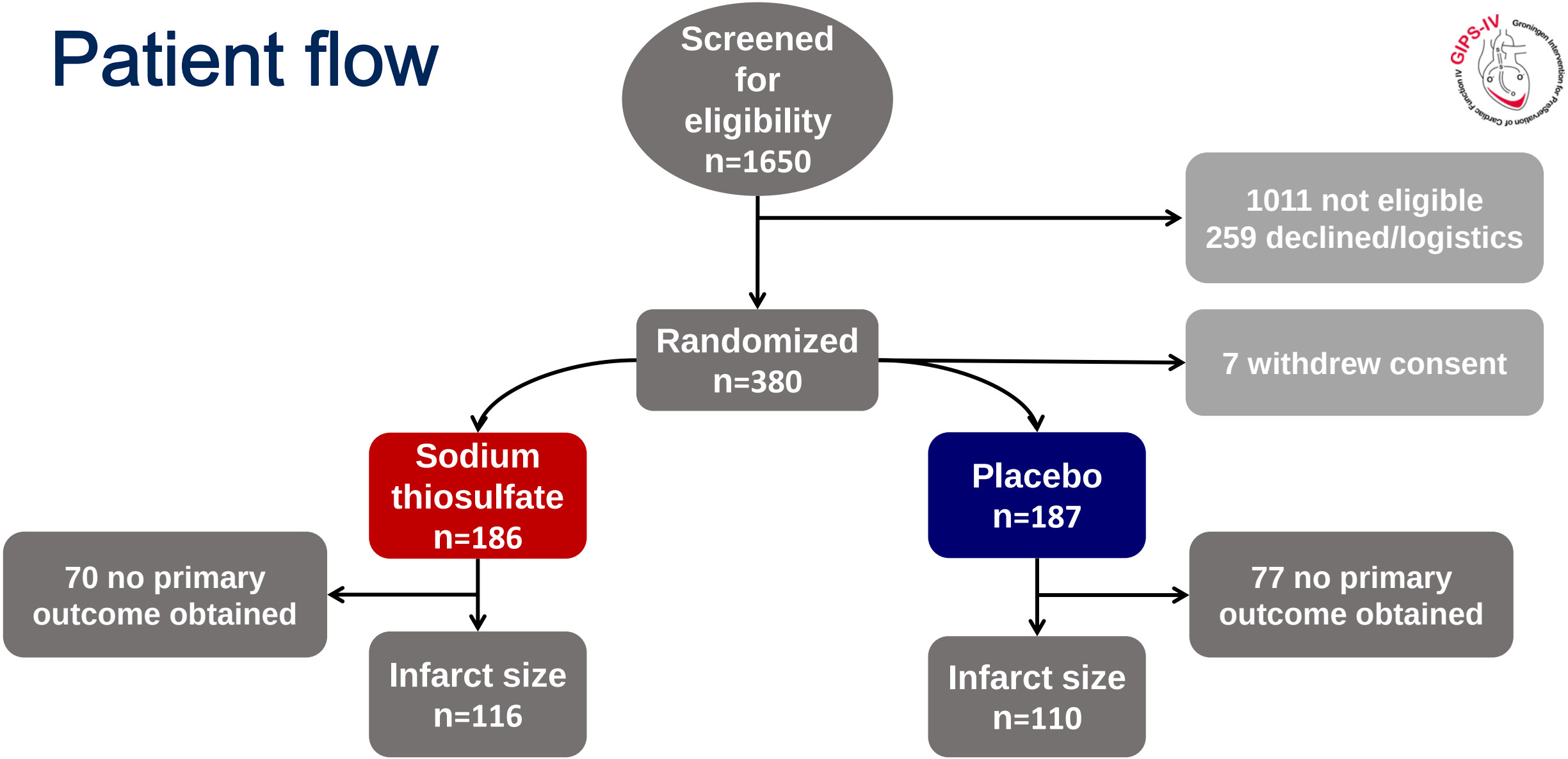
- 2-sided α=0.05
- anticipated infarct size: 9% (SD 7.9)
- anticipated drop-out: 33%

power: 85%
difference in infarct size: 3%

Study size

- 380 patients to obtain 250 evaluable primary outcomes

Patient flow



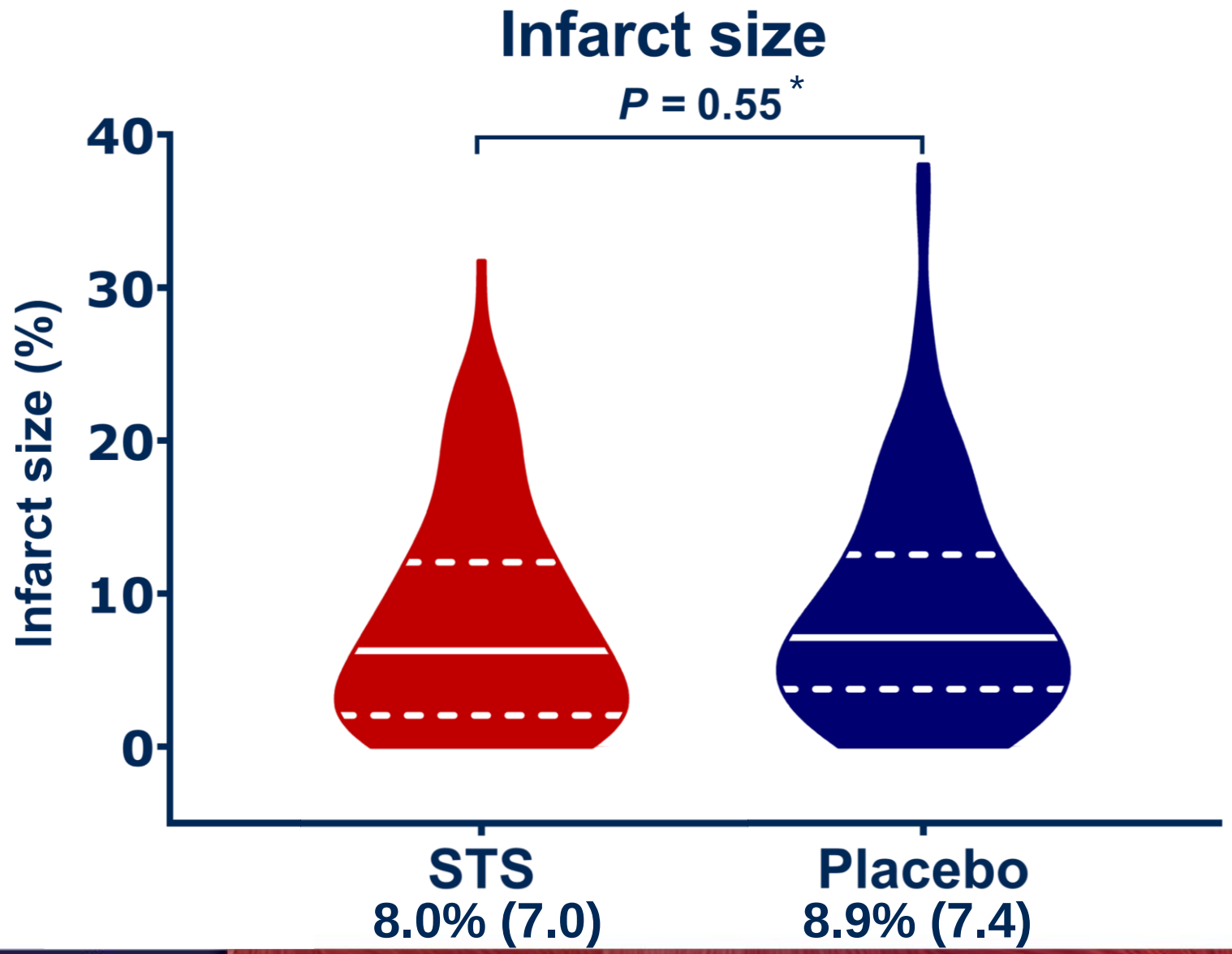
Baseline characteristics

	STS (n=186)	Placebo (n=187)
Age	62 (12)	62 (12)
Female sex	25%	21%
Caucasian ethnicity	97%	97%
Hypertension	46%	44%
Dyslipidemia	36%	36%
Diabetes Mellitus	12%	15%
Killip class I	97%	97%
Creatinine (µmol/L)	75 (65, 86)	75 (64, 86)
CK (U/L)	127 (82, 211)	134 (90, 232)
CK-MB activity (U/L)	15 (12, 20)	16 (13, 23)
NT-proBNP (ng/L)	106 (40, 221)	87 (43, 216)

Procedural characteristics

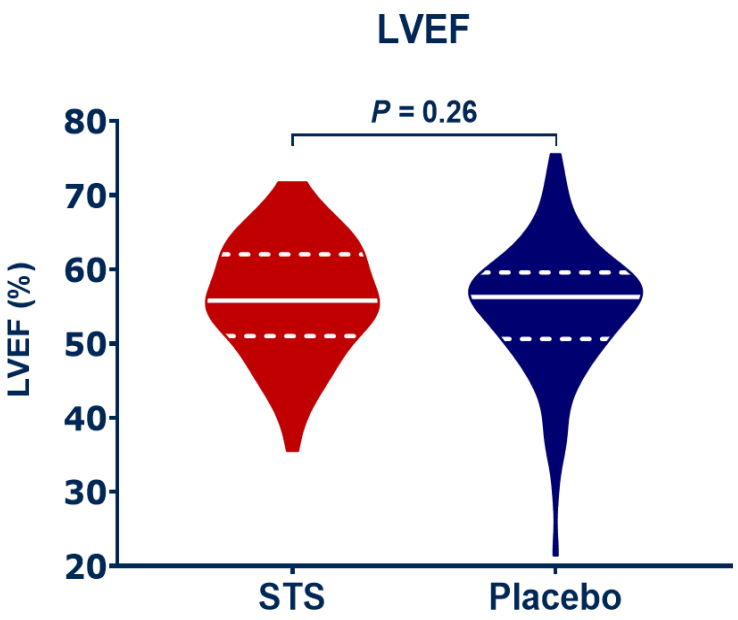
	STS (n=186)	Placebo (n=187)
Ischemic time (min)	133 (97, 203)	147 (104, 233)
Single vessel disease	55%	49%
Proximal laesion	41%	41%
Culprit in LAD	41%	41%
TIMI flow pre-PCI 0/1	67%	65%
Treated with PCI	97%	94%
TIMI flow post-PCI 3	93%	92%
Distal embolization	9%	6%

Primary outcome



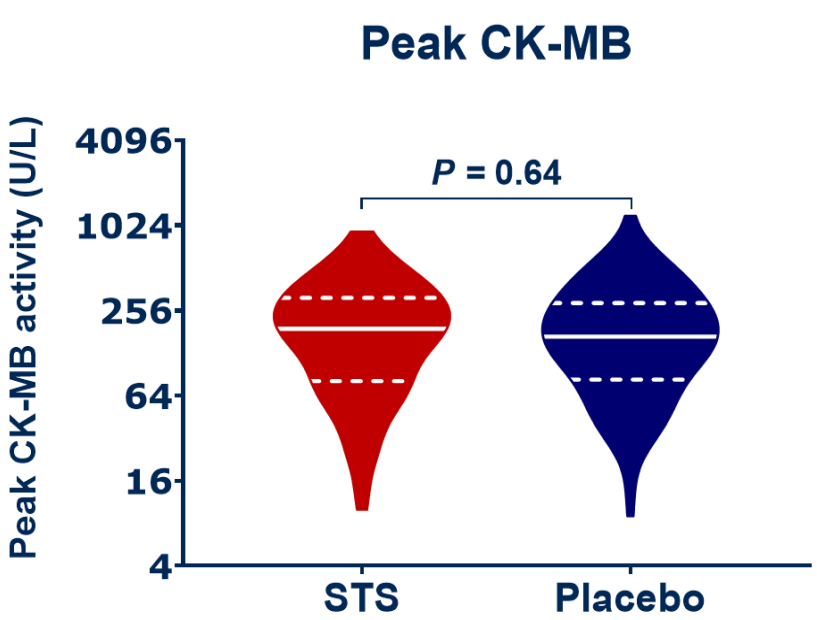
*analyzed with Beta Regression

Secondary outcomes



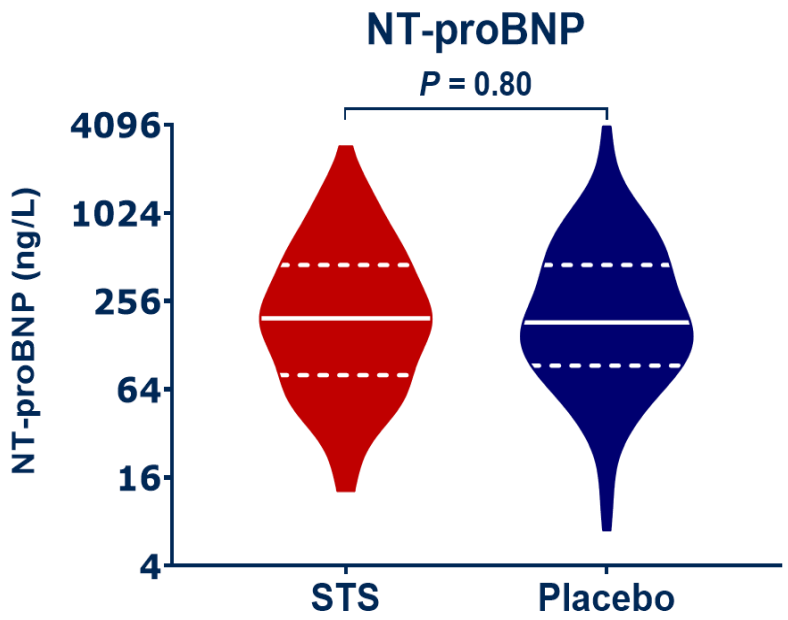
STS 56.1% (7.6)

Placebo 54.9% (8.7)



STS 191 (81, 315) U/L

Placebo 168 (84, 289) U/L



STS 195 (80, 452) ng/L

Placebo 183 (97, 445) ng/L

Clinical events

	STS (n=186)	Placebo (n=187)	*P*-value
Major adverse cardiovascular events	6	11	0.22
Cardiovascular mortality	1	2	0.57
Non-cardiovascular mortality	1	0	0.32
STEMI	2	6	0.16
NSTEMI	1	3	0.32
Unscheduled revascularization	4	5	0.74
Stent thrombosis	2	3	0.66
Stroke	1	0	0.32
Hospitalization for chest pain	6	3	0.31

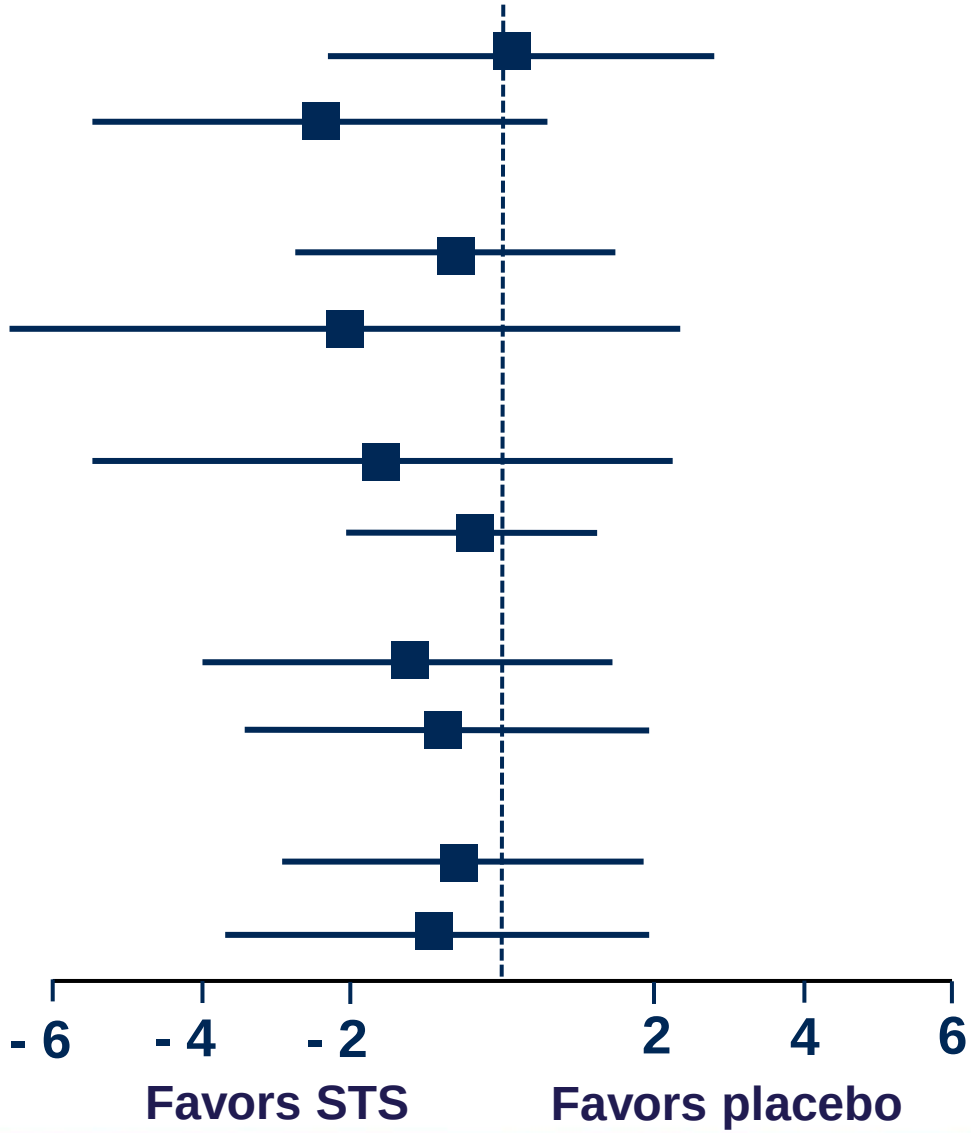
Safety

	STS (n=186)	Placebo (n=187)	*P*-value
Serious adverse events, total number	**18**	**18**	**0.99**
New-onset nausea*	**22%**	**6%**	**<0.001**
New-onset nausea without antiemetics	33%	12%	0.002
New-onset nausea with antiemetics	14%	3%	0.002
New-onset vomiting*	**14%**	**2%**	**<0.001**
New-onset vomiting without antiemetics	17%	3%	0.005
New-onset vomiting with antiemetics	11%	2%	0.004

*data shown for first dose

Subgroup analysis

Age ≤ median	58	66
Age > median	58	44
Male sex	91	94
Female sex	25	16
Anterior MI	44	43
Non-anterior MI	72	67
Ischemic time ≤ median	61	53
Ischemic time > median	52	54
TIMI flow pre-PCI 0/1	76	79
TIMI flow pre-PCI 2/3	40	31



Conclusions

Sodium thiosulfate at reperfusion:

- ➢ is safe to administer in patients presenting with STEMI
- ➢ does not reduce infarct size

Our results do not exclude H_2S as potential cardioprotective therapy

Targeting I/R-injury in humans remains challenging

Investigators & Committees

Participating sites & Principal investigator

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- P. van der Harst

University Medical Center Utrecht
- M. Voskuil

Treant Hospital, location Scheper
- R.L. Anthonio

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Monitoring
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Bentracimab Immediately and Significantly Reverses the Antiplatelet Effects of Ticagrelor in Older People

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| Heart & Vascular Center |

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

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This trial was funded by PhaseBio.

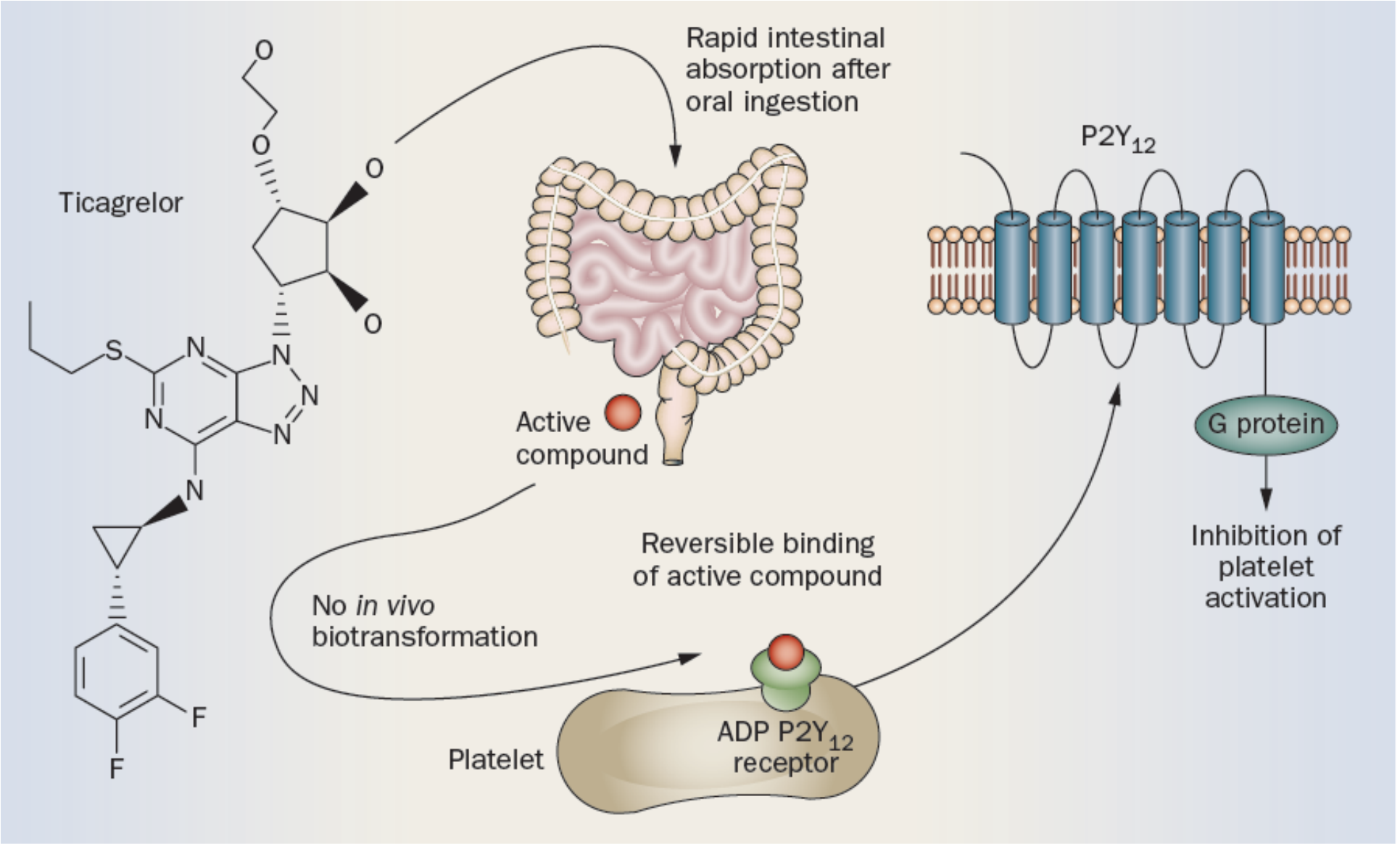
This presentation includes off-label and investigational uses of drugs.

Ticagrelor: Substantial Data, with Broad Label

- Ticagrelor is an oral $P2Y_{12}$ inhibitor that is effective (and FDA-approved) in patients with acute coronary syndromes, prior myocardial infarction, high-risk coronary artery disease, transient ischemic attack, and stroke, based on PLATO,[1,2] PEGASUS,[3,4] THEMIS,[5,6] THEMIS-PCI,[5,7] and THALES.[8]
- As with other antiplatelet drugs, spontaneous major bleeding and bleeding associated with urgent or emergent invasive procedures are concerns.
- The antiplatelet effects of ticagrelor cannot be reversed with platelet transfusion. Therefore, a rapid-acting reversal agent would be useful.

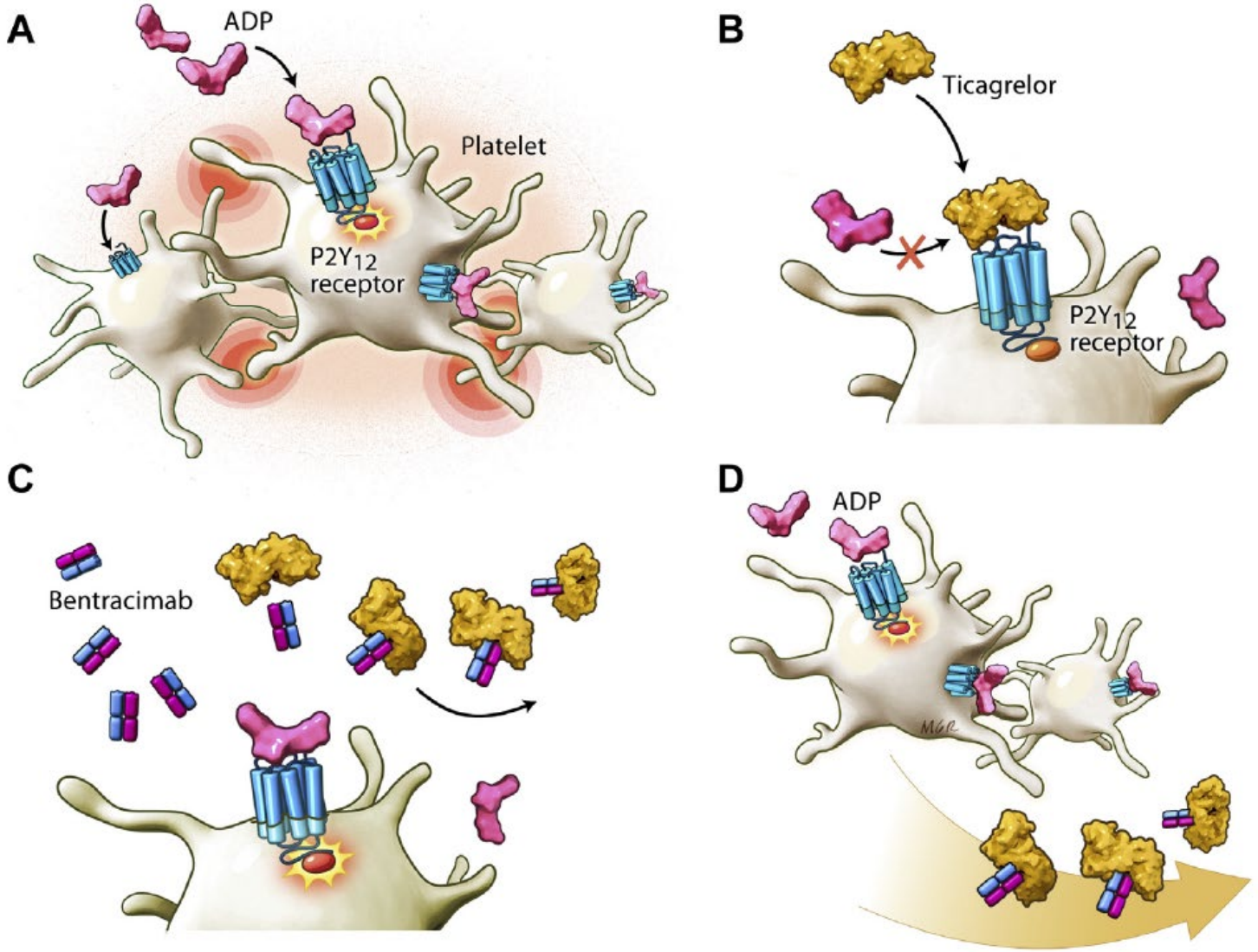
[1]James S, Akerblom A, Cannon CP, et al. *Am Heart J*. 2009;157:599-605.
[2]Wallentin L, Becker RC, Budaj A, et al. *N Engl J Med.* 2009;361:1045-57.
[3]Bonaca MP, Bhatt DL, Braunwald E, et al. *Am Heart J*. 2014;167:437-44.
[4]Bonaca MP, Bhatt DL, Cohen M, et al. *N Engl J Med*. 2015;372:1791-800.
[5]Bhatt DL, Steg PG, et al. *Clinical Cardiology* 2019; 42: 498-505.
[6]Steg PG, Bhatt DL, et al. *N Engl J Med.* 2019;381:1309-1320.
[7]Bhatt DL, Steg PG, et al. *Lancet*. 2019;394:1169-1180.
[8]Johnston SC, Amarenco P, et al. *N Engl J Med* 2020;383:207-217.

Ticagrelor: Reversible Mechanism of Action



Bhatt DL. ***Nature Reviews Cardiology*****. 2009;6:737-38.**

Bentracimab: An Intravenous Monoclonal Antibody



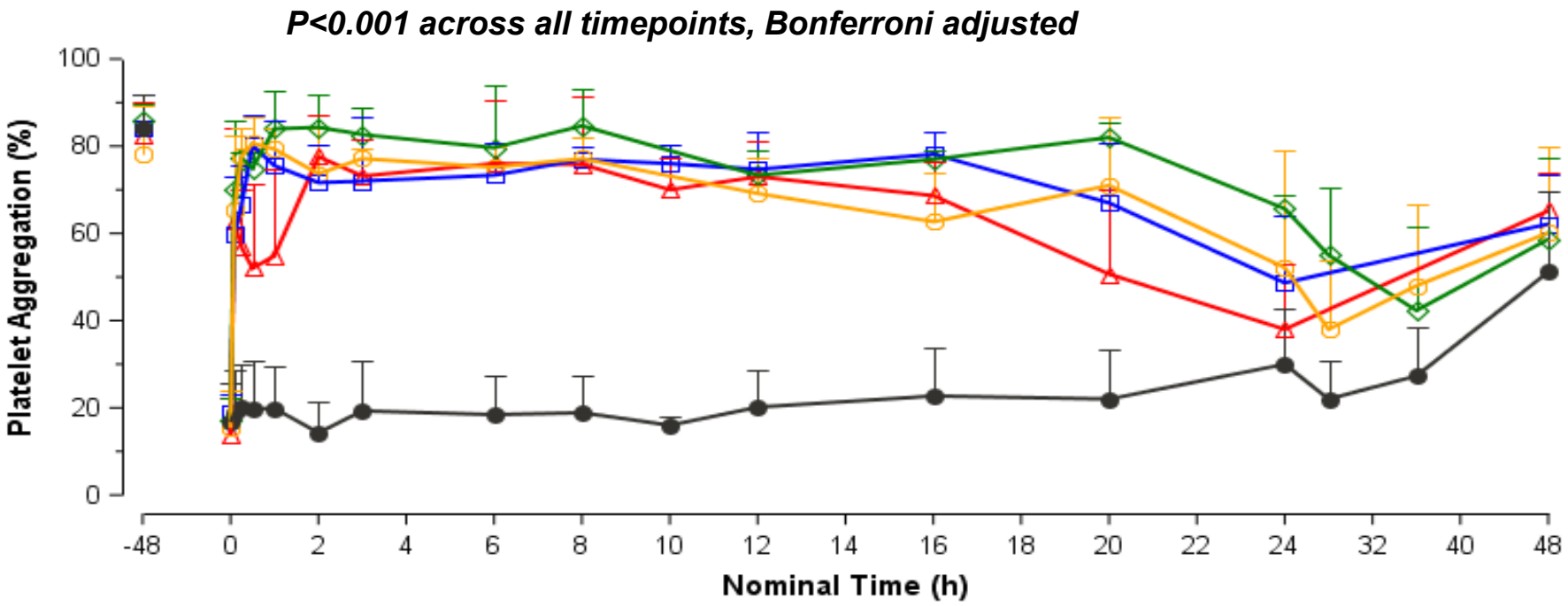
The P2Y12 receptor is activated by adenosine diphosphate (ADP) (A).

On platelets, ticagrelor reversibly binds to the P2Y12 receptor. This induces a conformational change which prevents ADP from signaling through to the P2Y12 receptor, inhibiting platelet activation (B).

Bentracimab is a recombinant human IgG1 monoclonal antibody fragment that binds to free ticagrelor with high affinity and specificity. This allows ADP to activate platelets while the bentracimab:ticagrelor complex is eliminated from the bloodstream (C&D).

Ha ACT, Bhatt DL, Rutka JT, Johnston SC, Mazer CD, Verma S. *J Am Coll Cardiol*. 2021;78:1372-1384.

Immediate Onset and Sustained Duration of Ticagrelor Reversal Using Bentracimab (formerly PB2452)



P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h
7	0.040	0.040	0.131	0.037	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.224
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020

Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected. P-values for time point 24 hours or above are not significant.

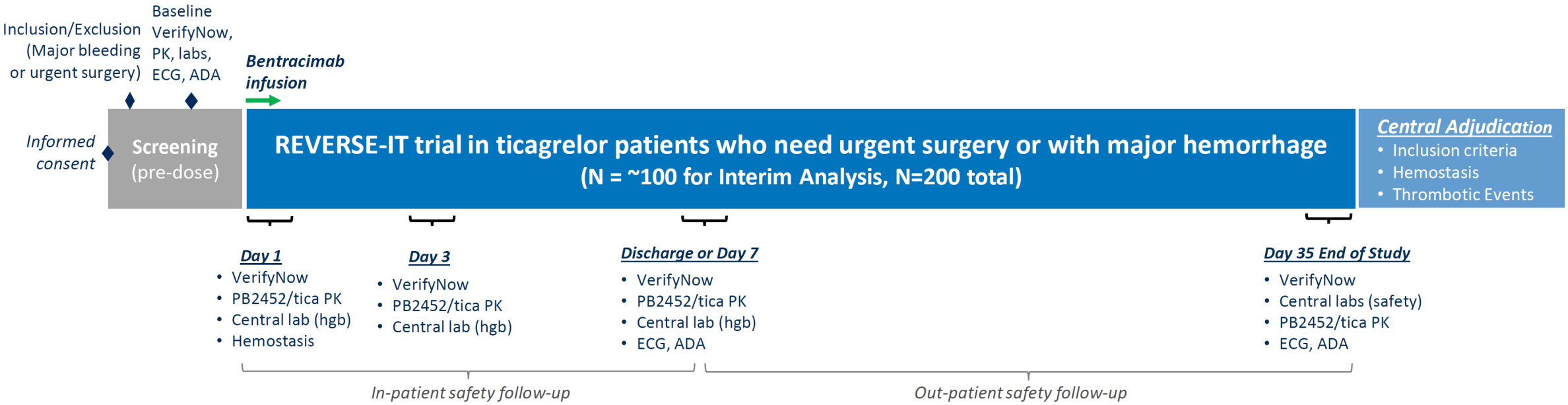
1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion** of 18 g bentracimab.
2. Significant reversal was observed 5 minutes after initiation of bentracimab infusion.
3. Duration of reversal was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion.

PB2452 18g(C7)
PB2452 18g(C8)
PB2452 18g(C9)
PB2452 18g(C10)
Placebo (C7-10)

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019; 380:1825-1833. ACC LBCT 2019.

LTA= light transmittance aggregometry; ADP is the agonist

REVERSE-IT: Phase 3 Interim Analysis Performed



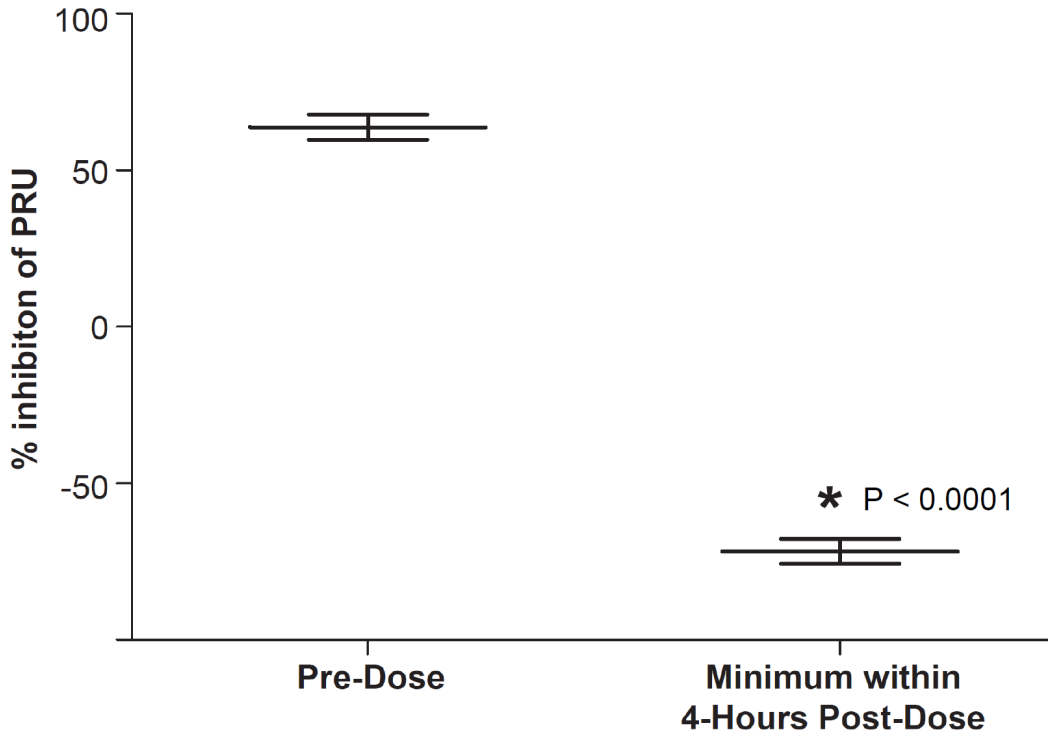
REVERSE-IT Study Design

Multicenter, open-label, prospective single-arm study **of reversal of the antiplatelet effects of ticagrelor with bentracimab in at least 200 patients who present with uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedures. Enrollment is ongoing in North America and Europe. Patients with use of ticagrelor within the prior 3 days who require urgent ticagrelor reversal are eligible for enrollment. Bentracimab was granted Breakthrough Therapy designation by the FDA and PRIME (priority medicines) designation by the European Medicines Agency, and in consultation with them, we performed this *prespecified, interim analysis* to support a BLA submission for an accelerated (conditional) approval.**

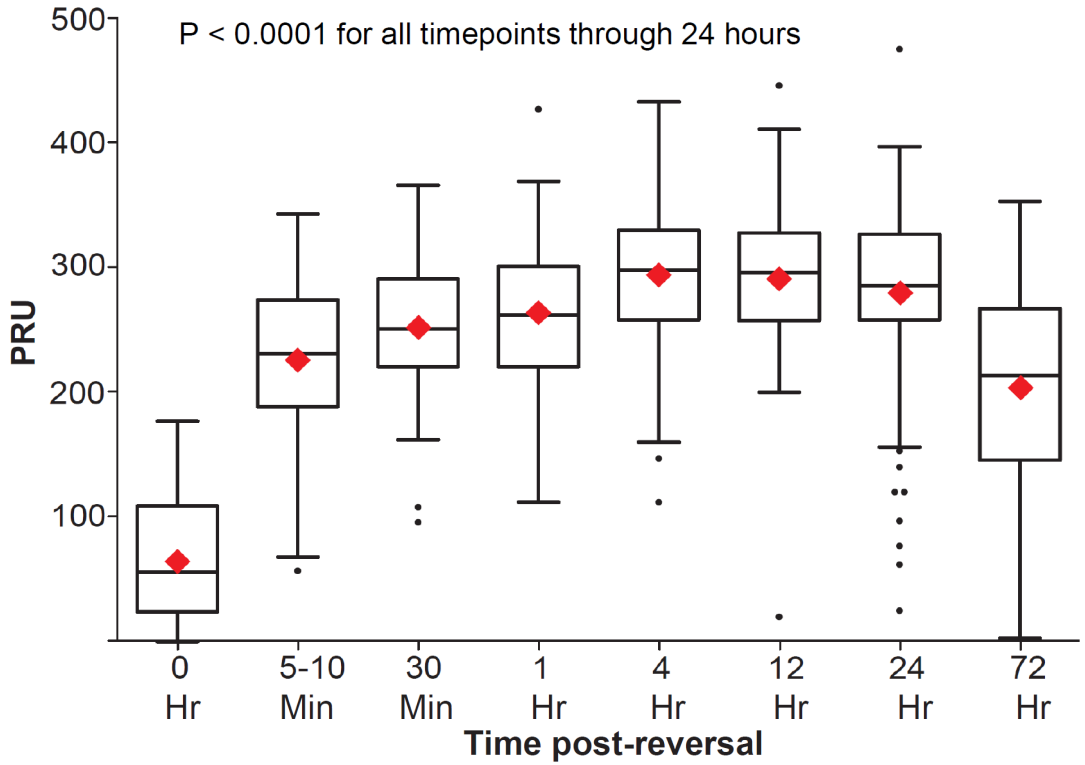
Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Platelet Function Tests

Percent Inhibition of PRU



PRU Analysis of Reversal



Ticagrelor Reversal with VerifyNow PRU. Ticagrelor reversal is shown as a reduction in % inhibition of PRU or PRI and as an increase in PRU or platelet reactivity index at multiple timepoints post-treatment. Shown is the comparison of % inhibition of PRU pre-treatment and the minimum % inhibition of PRU within 4 hours of initiation of bentracimab infusion (left). Onset and duration of ticagrelor reversal in bentracimab-treated patients observed as an increase in PRU with P value at each timepoint Bonferroni adjusted (right).

Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Adjudicated Surgical Hemostasis

Hemostasis in Surgical Patients	**n (%)**
Adjudicated achieved hemostasis (N=113)	113 (100.0)
GUSTO Mild	75 (66.4)
GUSTO Moderate	38 (33.6)
GUSTO Severe	0 (0)
Investigator-reported achieved hemostasis (N=142)	135 (95.1)
Normal or mildly abnormal bleeding	110 (77.5)
Moderately abnormal	25 (17.6)
Severely abnormal or unknown	7 (4.93)
Blood Product Transfusions	**n (%)**
Total blood transfusions (pRBCs or whole blood)	56 (39.04)
Blood transfusions for bleeding event	10 (7.04)
Total platelets transfusions	19 (13.4)
Platelet transfusions for bleeding event	6 (4.22)
Other Surgical Outcomes	
Restarted $P2Y_{12}$ inhibition, n (%)	111 (74%)
Time to restart (median), days (min, max)	2 (0, 22)
Total mortality, n (%)	4 (2.8)

pRBC, packed red blood cells. Investigators were required to specify in case report forms whether allogeneic blood and platelet products were transfused for bleeding events or other routine perioperative use. Total transfusions and transfusions for bleeding events are shown above.

Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Adjudicated Thrombotic Events

Adjudicated Thrombotic Events Occurring Post-Reversal

Type of Event	Patient Type	Days from Bentracimab and Surgery	P2Y12 Restarted Before Event	Related to Bentracimab
51 yr old man, s/p CABG	Myocardial infarction	7	Yes	No
78 yr old woman, s/p CABG	Transient ischemic attack	2	Yes	No
70 yr old man, s/p CABG	Lacunar stroke	1	No	No
58 yr old man, s/p CABG	Anterior, inferior STEMI with total graft occlusion	1	No	No
69 yr old man, s/p CABG, intraortic balloon pump, and thrombectomy	RLE arterial thromboembolism	1	No	No
73 yr of woman, s/p CABG	Acute ischemic stroke	5	No	No
44 yr old male, s/p CABG	Acute coronary syndrome with graft failure	29	Yes	No
47 yr old man, s/p CABG +aortic dissection repair	Acute ischemic right leg immediately post-op	1	No	No

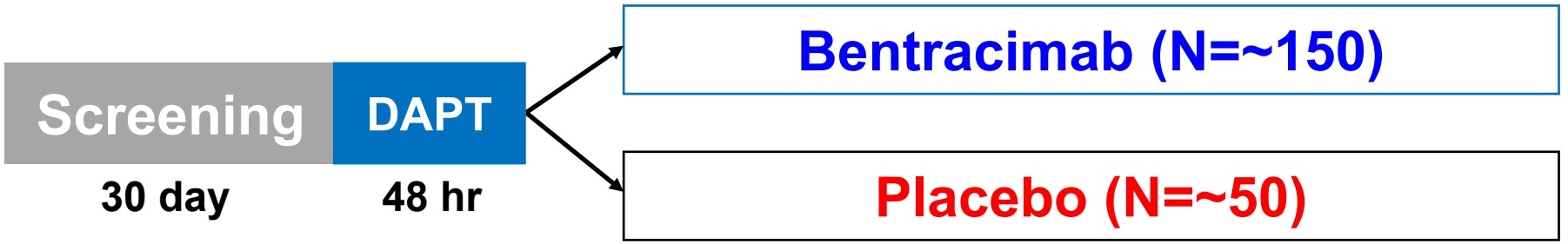
Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Interim Analysis Summary

- **Bentracimab**, a specific reversal agent for ticagrelor, provided immediate and sustained reversal of ticagrelor's antiplatelet effects, in ticagrelor-treated patients undergoing invasive procedures or with major bleeding.
- Rates of effective hemostasis were adjudicated as good or excellent in >90% of cases, with no drug-related serious adverse events or allergic or infusion-related reactions.
- The benefits were consistent in all prespecified subgroups, including those undergoing surgery or with major bleeding.

Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

Phase 2B Study Design



Randomized, double-blind, placebo-controlled trial (3 active:1 placebo)

- 50-80 year-old volunteers pretreated with ticagrelor and aspirin for 48 hours
- Primary endpoint - inhibition of PRU

Baseline Characteristics

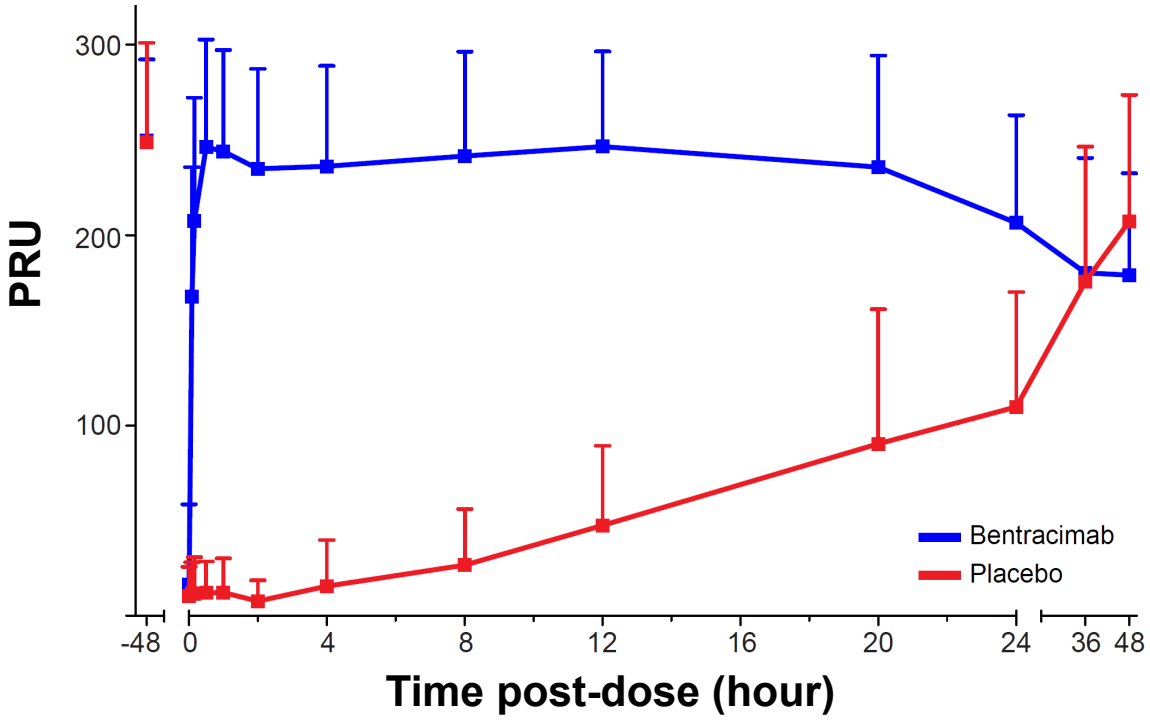
Characteristic Statistic	Placebo (N = 51)	Bentracimab (N = 154)	Total (N=205)
Age* [years]			
n	51	154	205
Mean (SD)	60.9 (6.76)	61.4 (6.90)	61.2 (6.85)
Median	60	61	61
Min, Max	50, 78	50, 80	50, 80
Age Group, n (%)			
<= 65 years	39 (76.47)	107 (69.48)	146 (71.22)
> 65 years	12 (23.53)	47 (30.52)	59 (28.78)
Sex, n (%)			
Male	21 (41.18)	82 (53.25)	103 (50.24)
Female	30 (58.82)	72 (46.75)	102 (49.76)
Ethnicity, n (%)			
Hispanic or Latino	7 (13.73)	18 (11.69)	25 (12.20)
Not Hispanic or Latino	44 (86.27)	136 (88.31)	180 (87.80)
Race, n (%)			
Asian	0	3 (1.95)	3 (1.46)
Black or African American	8 (15.69)	29 (18.83)	37 (18.05)
White	43 (84.31)	121 (78.57)	164 (80.00)
Other	0	1 (0.65)	1 (0.49)

Baseline Characteristics

Characteristic Statistic	Placebo (N = 51)	Bentracimab (N = 154)	Total (N=205)
Renal Group, n (%)			
Normal	16 (31.37)	46 (29.87)	62 (30.24)
Mild	30 (58.82)	91 (59.09)	121 (59.02)
Moderate	4 (7.84)	14 (9.09)	18 (8.78)
Country, n (%)			
Canada	8 (15.69)	23 (14.94)	31 (15.12)
United States	43 (84.31)	131 (85.06)	174 (84.88)
Weight [kg]			
n	51	154	205
Mean (SD)	80.4 (12.93)	80.8 (14.77)	80.7 (14.30)
Median	83.1	81.6	81.6
Min, Max	51.0, 106.0	51.0, 117.5	51.0, 117.5
Height [cm]			
n	51	154	205
Mean (SD)	168.3 (9.99)	169.9 (10.17)	169.5 (10.12)
Median	167.6	170.0	169.5
Min, Max	149.0, 188.2	148.8, 194.5	148.8, 194.5
BMI [kg/m^2]			
n	51	154	205
Mean (SD)	28.3 (3.49)	27.9 (3.71)	28.0 (3.65)
Median	28.3	27.8	27.9

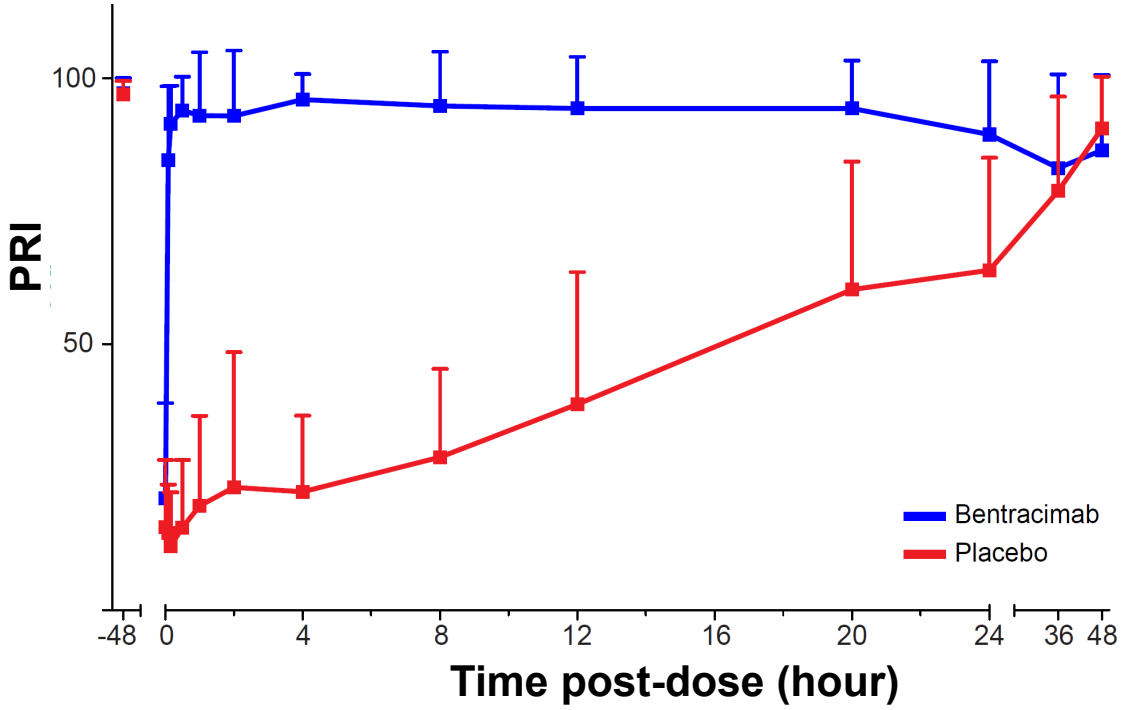
Immediate, Sustained Ticagrelor Reversal with Bentracimab
(VerifyNow PRU and VASP PRI Assays)

PRU analysis
(Bentracimab vs Placebo 0-48 hours)



Timepoint	5 min	10 min	30 min	1 hr	4 hr	12 hr	20 hr	24 hr	36 hr	48 hr
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.1102	0.0127

PRI analysis
(Bentracimab vs Placebo 0-48 hours)

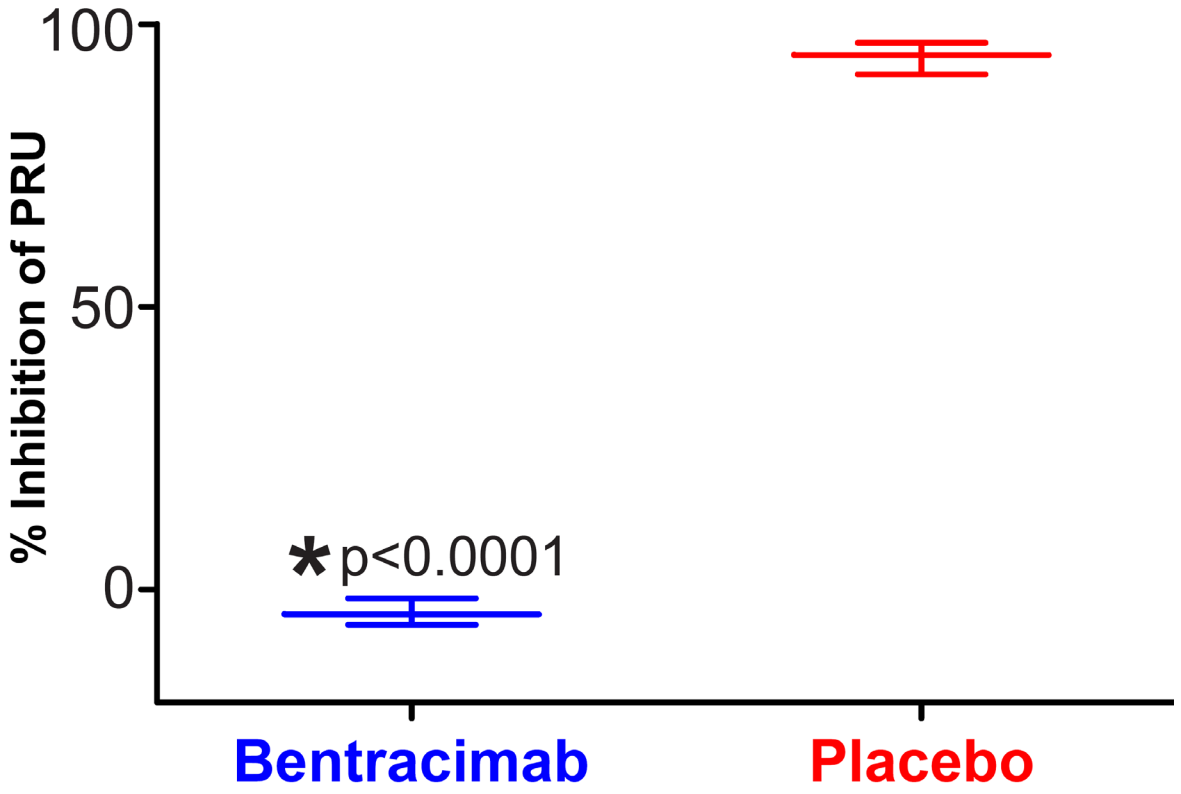


Timepoint	5 min	10 min	30 min	1 hr	4 hr	12 hr	20 hr	24 hr	36 hr	48 hr
P value	0.0572	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.2802	0.4562

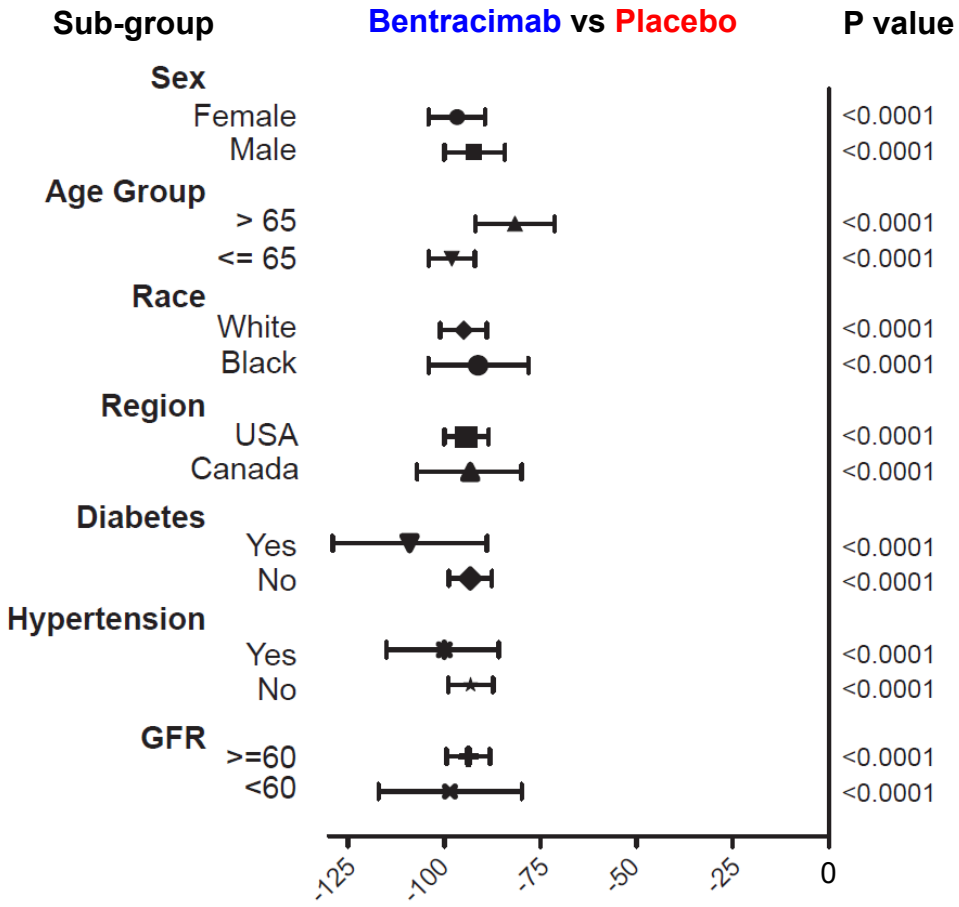
Bentracimab achieved immediate and sustained reversal in 50-80 year-olds pretreated with DAPT

Primary Endpoint and Subgroup Analysis

Primary Endpoint Analysis
(Minimum % inhibition of PRU within 4 hrs)

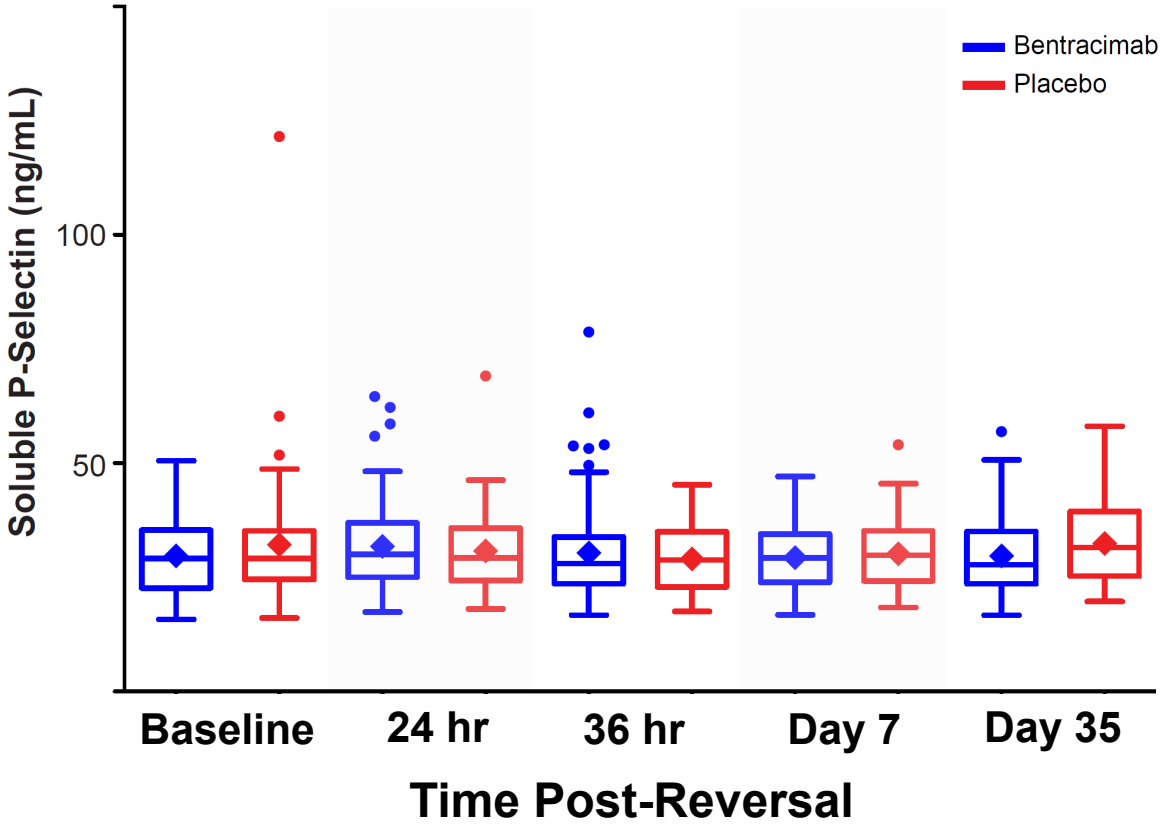


Forest Plot of Treatment Difference
(Mean change in minimum % inhibition of PRU)

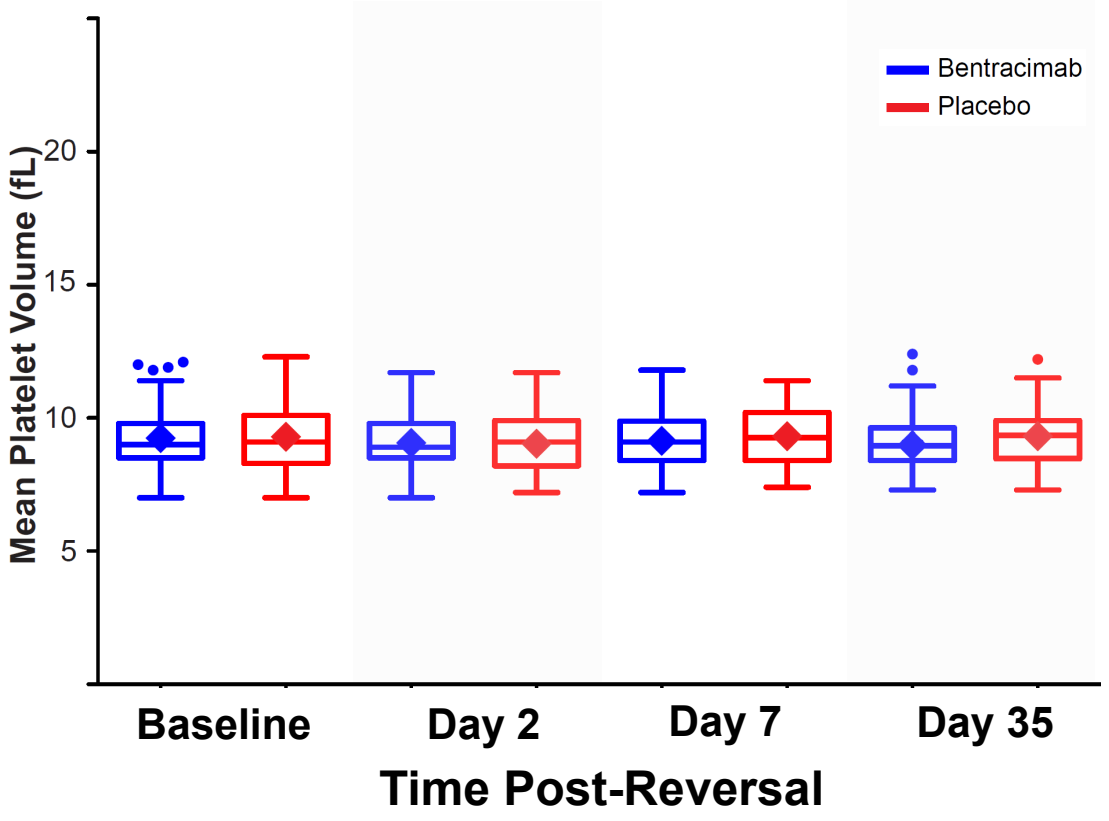


Markers of Platelet Activation

P-Selectin Analysis



Mean Platelet Volume Analysis



No evidence of elevated platelet activation post-reversal in Bentracimab or Placebo groups

Bentracimab Safety Profile

Treatment Emergent Adverse Events in >1 Subject

TEAEs	Placebo N = 51 n (%)	Bentracimab* N = 154 n (%)
Headache	4 (7.84)	6 (3.90)
Ecchymosis	2 (3.92)	6 (3.90)
Contusion	2 (3.92)	5 (3.25)
Vessel puncture bruise	1 (1.96)	4 (2.60)
Nausea	2 (3.92)	3 (1.95)
Diarrhea	1 (1.96)	3 (1.95)
Edema	1 (1.96)	2 (1.30)
Dizziness	1 (1.96)	2 (1.30)
Infusion site extravasation	0	2 (1.30)
Pain in extremity	0	2 (1.30)
Asymptomatic COVID-19	0	2 (1.30)
Catheter site bruise	1 (1.96)	1 (0.65)
Constipation	1 (1.96)	1 (0.65)
Occult blood	1 (1.96)	1 (0.65)
Hematochezia	2 (3.92)	0
Hyperglycemia	2 (3.92)	0

*There was no significant difference between Bentracimab and Placebo for any TEAE, P=0.52

All Serious Adverse Events

Preferred Term	Placebo (N=51) n (%)	Bentracimab (N=153) n (%)
Total SAEs	1	0
Drug-related SAEs	0	0
Unrelated SAEs	1	0
Car accident	1	0

- **No drug-related SAE's**
- **No thrombotic events**

Limitations

- We studied 50-80 year-old volunteers and not patients with known coronary artery disease, although no reason to believe **bentracimab** would behave differently.
- The sample size was modest, although it was well-powered for pharmacodynamic endpoints, and all platelet assay results were consistent and highly statistically significant.
- This study was not designed to evaluate the impact of **bentracimab** on clinical bleeding events.

Conclusions

- Compared with placebo, **bentracimab** **significantly restored platelet function as measured** by multiple assays by binding and eliminating free ticagrelor and ticagrelor active metabolite.
- **No thrombotic events and no SAEs** reported in volunteers randomized to **bentracimab**, confirming the safety profile.
- Based on these data, **bentracimab** **appears to be a very promising option for ticagrelor reversal**.
- Assessment of **bentracimab's** clinical effect on patients with bleeding awaits completion of the **REVERSE-IT** study.

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

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BWH Heart & Vascular Center;
Professor of Medicine,
Harvard Medical School
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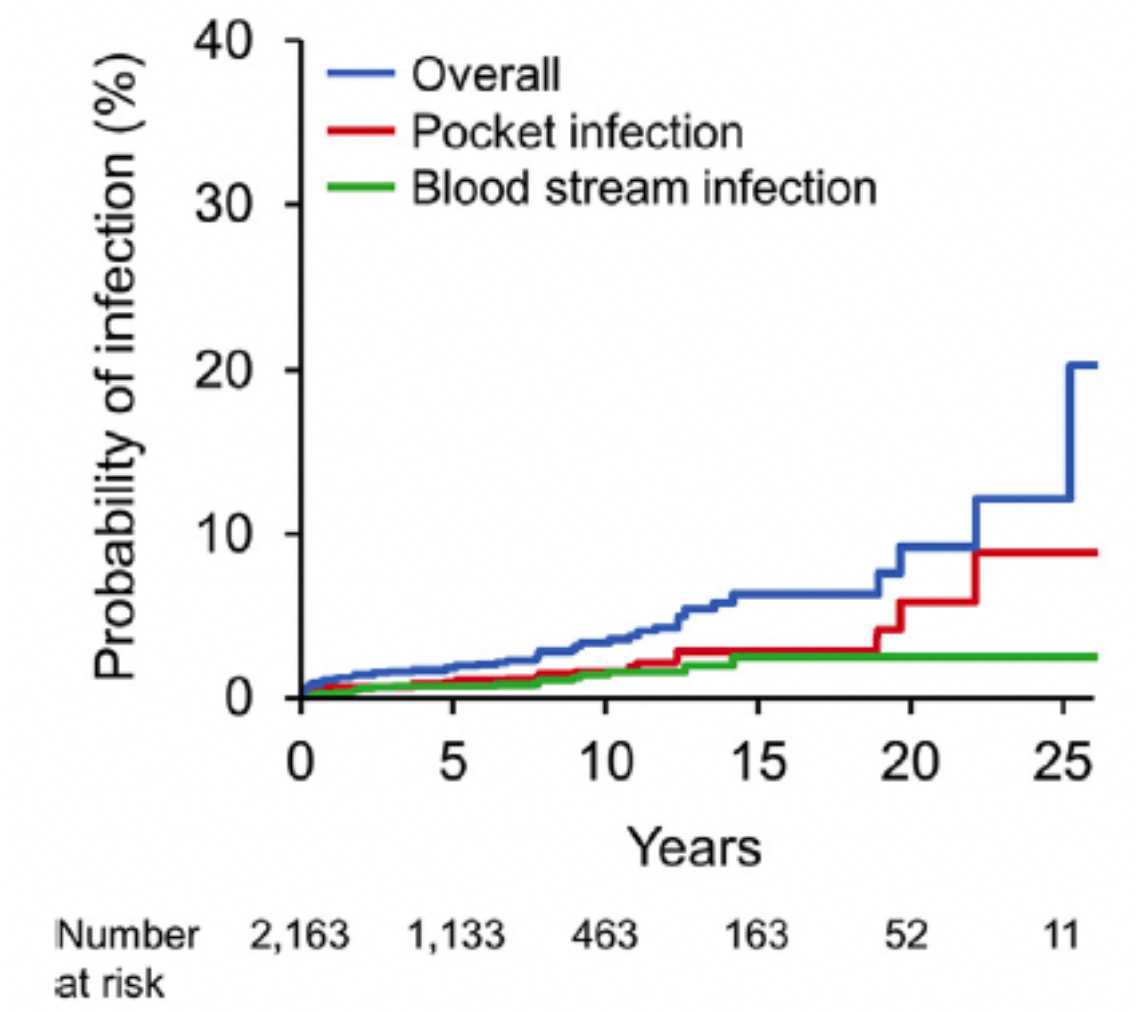
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Low Rates of Guideline Directed Care Associated with Higher Mortality Among Patients with Cardiac Implanted Electronic Device Infection

Sean D. Pokorney, Lindsay Zepel, Melissa A. Greiner, Vance G. Fowler, Jr., Eric Black-Maier, Robert K. Lewis, Donald D. Hegland, Christopher B. Granger, Laurence M. Epstein, Roger G. Carrillo, Bruce L. Wilkoff, Chantelle Hardy, Jonathan P. Piccini

Duke Heart Center

CIED Infection is Common in Clinical Practice



Overall Rate of CIED Infection

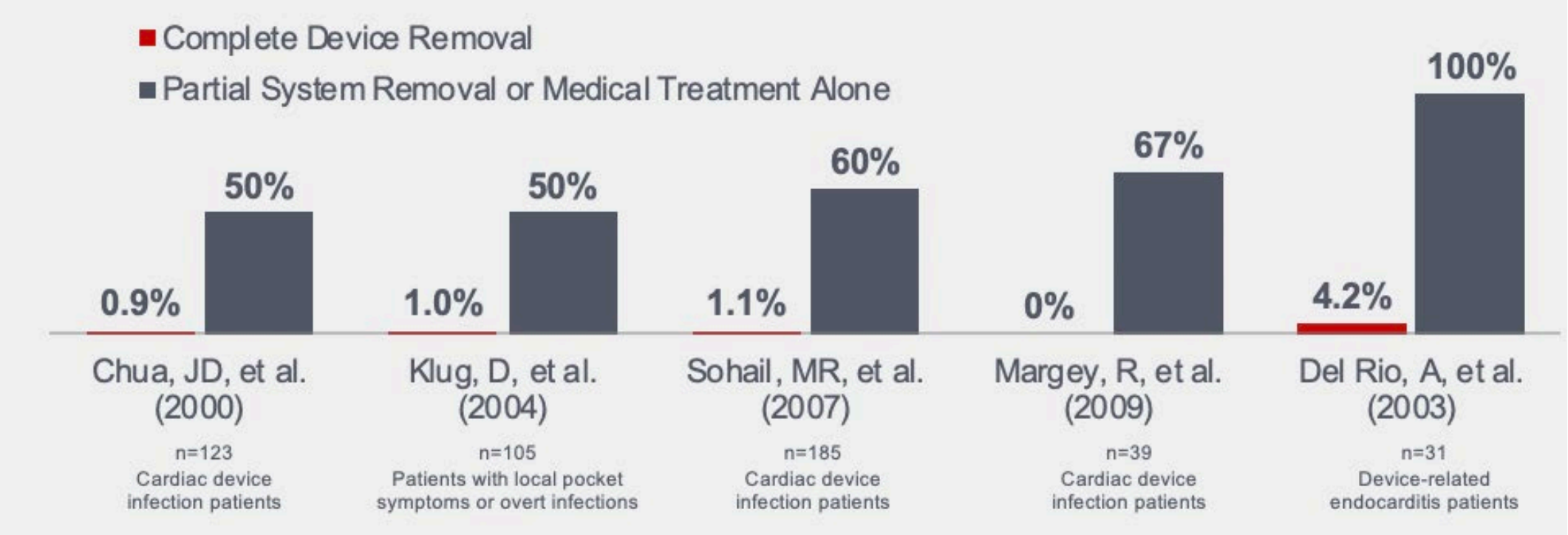
6.2% at 15 years

11.7% at 25 years

Duke Heart Center

Dai M, et al. *J Am Coll Cardiol EP* 2019;5:1071–80

Risk of Relapse Without Complete Removal is Very High



Infection relapse occurs in 50% to 100% of cases with partial removal or antibiotic treatment alone, compared to relapse of **0% to 4.2% with complete system removal**.

Duke Heart Center

Chua JD, et al. *Ann Intern Med*. 2000;133(8):604-608.
Klug D, et al. *Heart*. 2004;90(8):882-886.
Sohail MR, et al. *J Am Coll Cardiol*. 2007;49(18):1851-1859.
Margey R, et al. *Europace*. 2010;12(1):64-70.
del Rio A, et al. *Chest*. 2003;124(4):1451-1459.

Device Infections Require Complete Hardware Removal

I	B-NR

Complete device and lead removal is recommended for all patients with definite CIED system infection.

Heart Rhythm Society℠

American Heart Association

EUROPEAN SOCIETY OF CARDIOLOGY

BHRS British Heart Rhythm Society

EHRA

Duke Heart Center

GUIDELINE	RECOMMENDATIONS	
	Complete Extraction	Prompt Extraction
AHA 2010[A]	x	x
BHRS 2014[B]	x	x
ESC 2015[C]	x	
HRS 2017[D]	x	x
EHRA 2020[E]	x	x

A. Baddour LM. *Circulation*. 2010;121:458-477
B. Sandoe JA. *J Antimicrob Chemother*. 2015;70:325-59.
C. Habib G. *European Heart Journal.* 2015;36:3075–3128.
D. Kusomoto F. *Heart Rhythm*. 2017;14: e503-e551.
E. Blomström-Lundqvist C. *Europace*. 2020;22: 515–549

Methods

- 100% Medicare fee-for-service patients with Part D (1/2006-12/2019)
  - *de novo* CIED implant
  - CIED infection >12 months after implant
    - Endocarditis or infection of a device implant

      AND
    - Documented IV antibiotic therapy within 30 days after device infection
- Outcomes included diagnosis of device infection, device extraction, time to extraction, and all-cause mortality
- Time-varying multivariable Cox models to evaluate the association between extraction and mortality

Baseline Characteristics

	Overall (n=1,065,549)	CIED Infection (n=11,619)
Age, median in years	78	75
Female, %	522,877 (49.1)	4,610 (39.7)
Race, %		
White	929,276 (87.2)	8,981 (77.3)
Black	80,827 (7.6)	1,811 (15.6)
Comorbidities, %		
Dementia	120,890 (11.3)	1,393 (12.0)
Diabetes mellitus	525,584 (49.3)	7,937 (68.3)
Ischemic heart disease	846,343 (79.4)	10,570 (91.0)
Heart failure	691,251 (64.9)	10,108 (87.0)
Chronic obstructive pulmonary disease	585,915 (55.0)	8,206 (70.6)
Renal disease	403,603 (37.9)	8,197 (70.5)
Stroke/TIA	315,595 (29.6)	4,158 (35.8)
Device type, %		
CRT-D or CRT-P	114,695 (10.7)	1,401 (14.7)
Pacemaker	765,432 (71.8)	5,397 (56.8)
ICD	185,422 (17.4)	2,712 (28.5)

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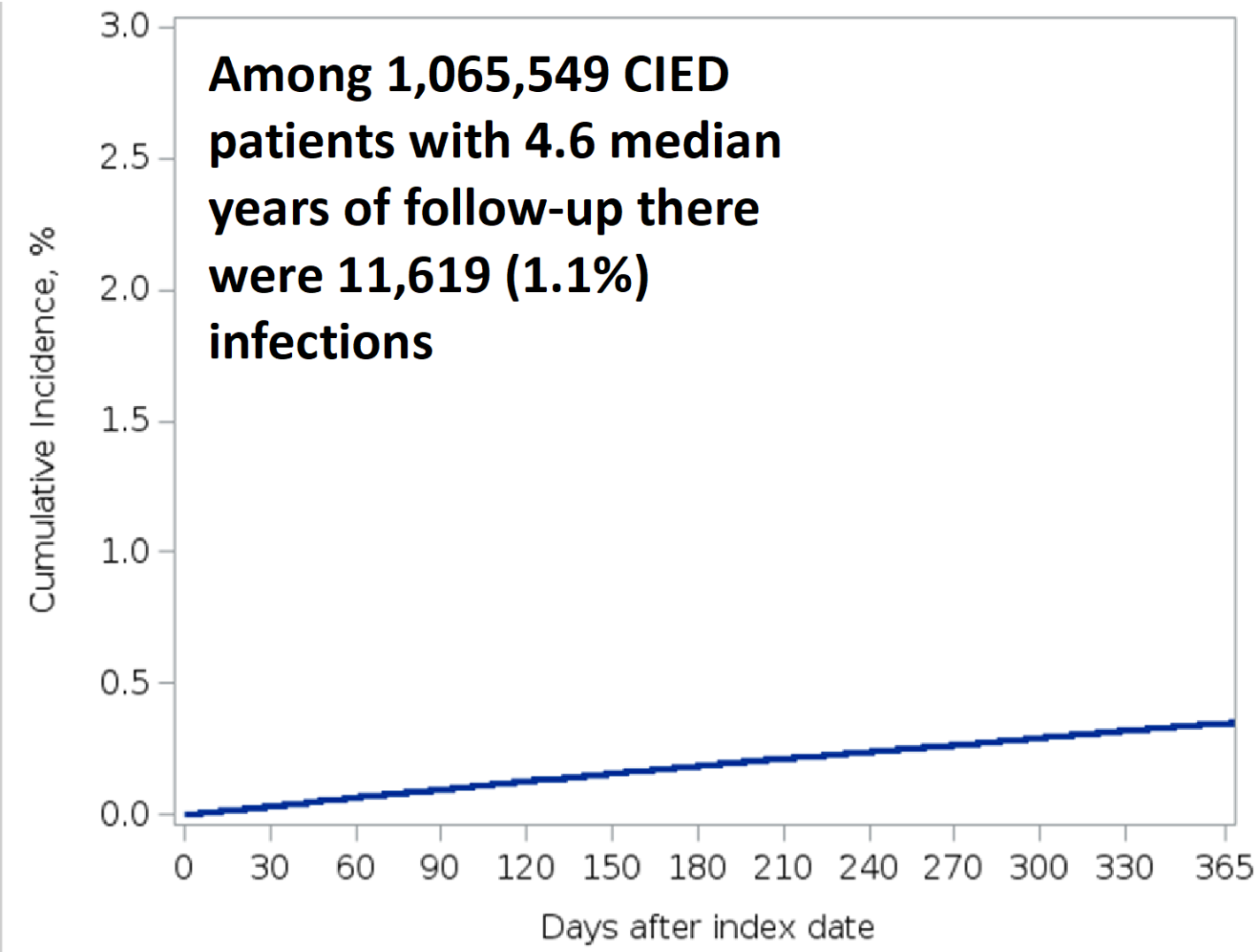
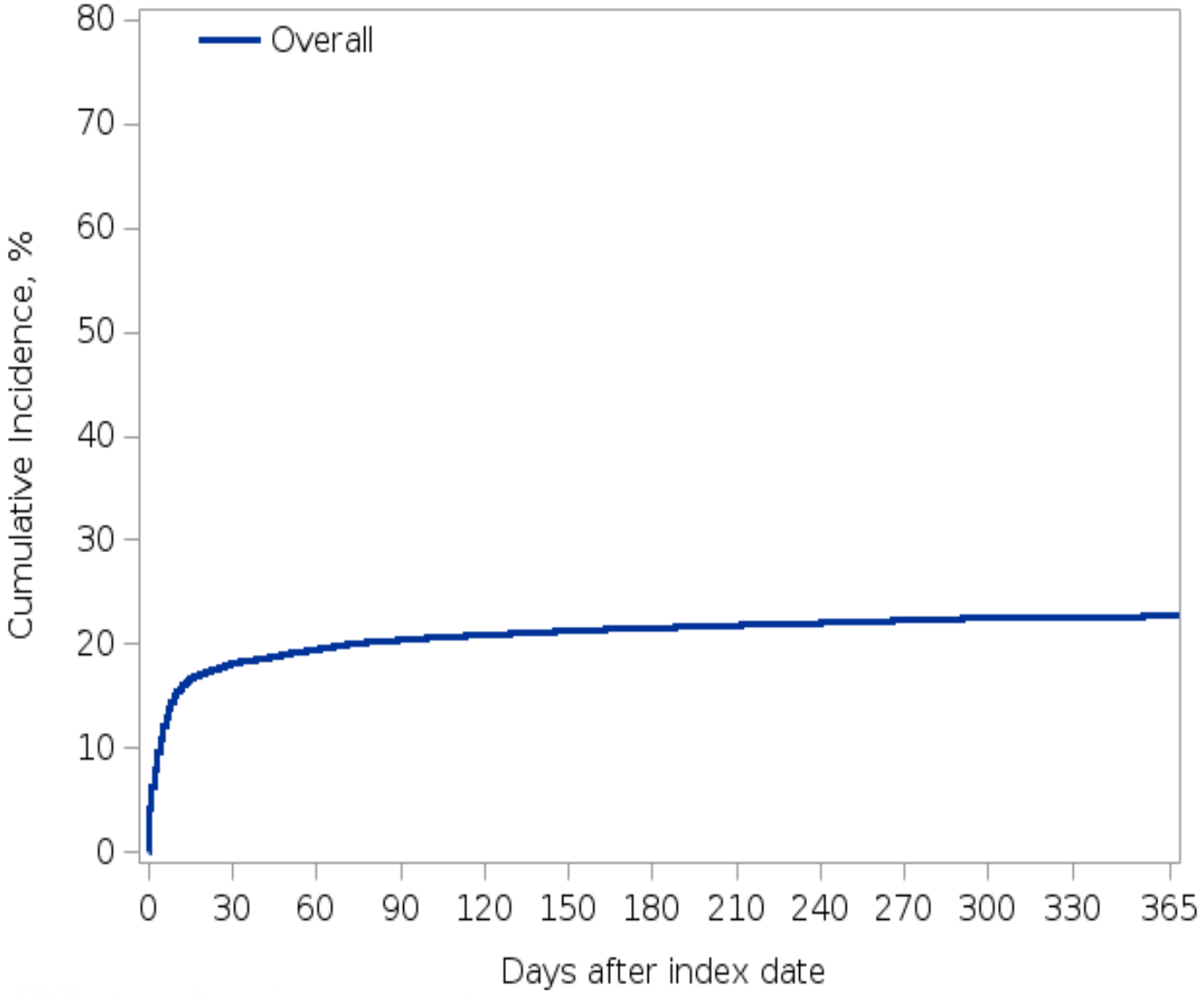
Cumulative Incidence of Infection



- Infection rates
  - 3,521 (0.3%) at 1 year post implant
  - 5,802 (0.6%) at 2 years post implant
  - 9,564 (1.1%) at 3 years post implant
- Infection occurred a mean 3.7±2.4 years after implant

Duke Heart Center

Cumulative Incidence of Extraction

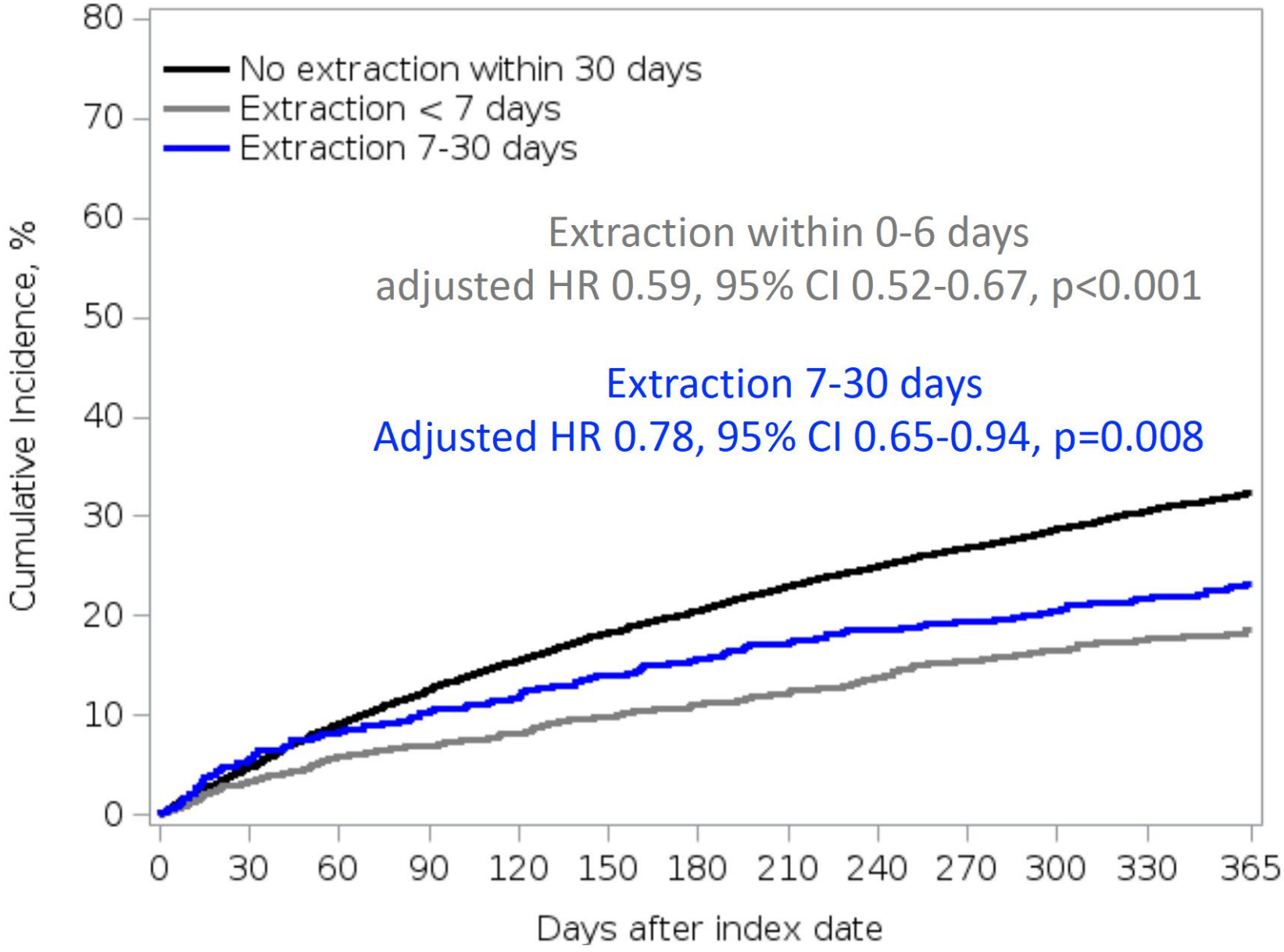


- Most patients did not have extraction within 30 days (81.8%, N=9,510)
- 13% (N=1,515) had extraction within 6 days of diagnosis
- Female patients (31% of extraction vs 41% of no extraction) and black patients (11% of extraction vs 17% of no extraction) were less likely to undergo extraction ($p<0.001$)

Duke Heart Center

Results: Cumulative Mortality by Extraction Time

- 1-year mortality was 32.4% for patients without extraction within 30 days
- Extraction versus no extraction had an association with lower mortality: HR 0.73 (95% CI 0.7-0.81)



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Strengths & Limitations

- Large, nationwide analysis
- Residual measured & unmeasured confounding may have influenced the mortality findings, despite adjusted modeling.
  - Dose-response to timing of extraction makes it less likely that confounding explains the mortality benefit with extraction.
- Strict definition for infection (device infection & antibiotics)
  - May underestimate magnitude of problem: 1 year infection rates are lower than reported in other series
- Only patients 65 and older
  - Decision-making is often more complex based on comorbidities, life expectancy, and high event rates in this population

Conclusions

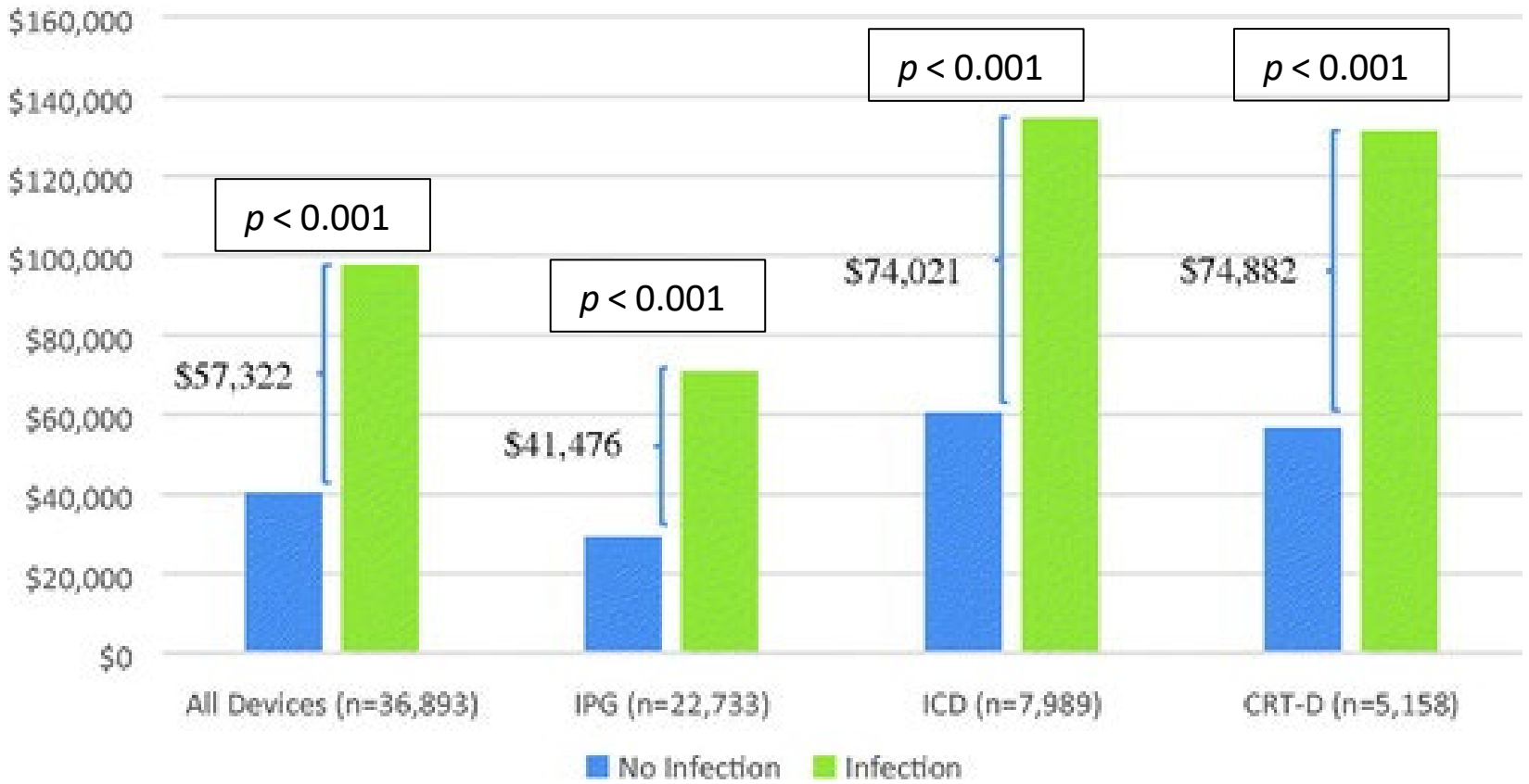
- Despite current guideline recommendations, only 1 in 5 patients with a CIED infection underwent extraction
- Female and black patients were less likely to undergo extraction.
- Extraction was associated with 27% lower hazard of mortality
- In a dose response fashion, earlier extraction was associated with 41% lower hazard of mortality, significantly lower compared with later extraction
- Quality improvement initiatives and care redesign programs are needed in order to improve the guideline-based care that CIED patients receive within health systems

Thank you

Back-Up Slides

Average US annual medical costs were 2.4x greater for CIED infection patients compared with no infection

One-Year Adjusted Expenditures for CIED Patients with and without a CDI by Device Type



Abbreviations. CIED, cardiac implantable electronic device; CDI, cardiac device infection; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; IPG, implantable pulse generator (pacemaker).

Duke Heart Center

Eby et al. Economic impact of cardiac implantable electronic device infections: cost analysis at one year in a large U.S. health insurer. J Med Econ 2020;23:698-705..

1,065,549
CIED patients
median age 78 years

Cumulative incidence of
CIED infection

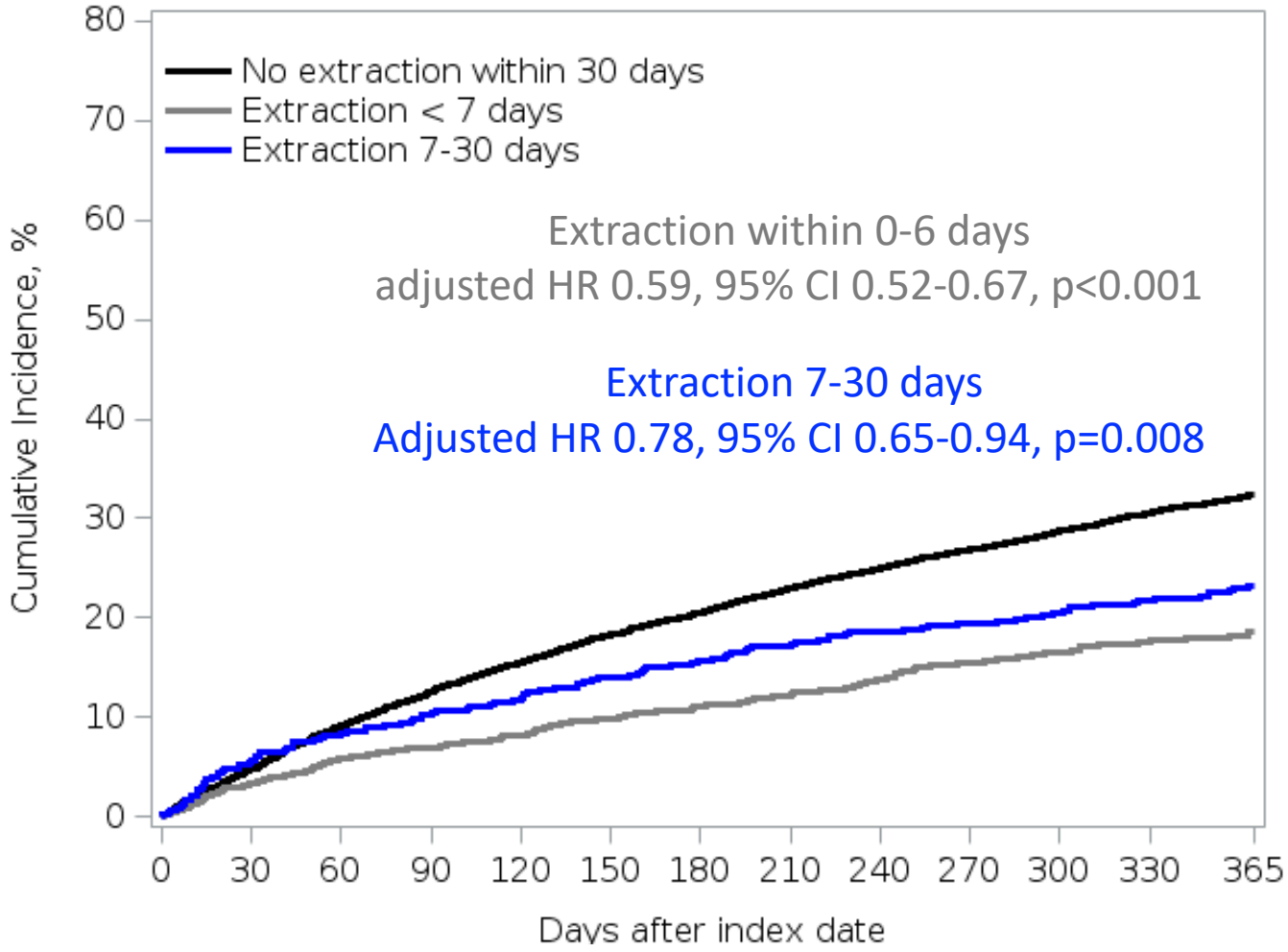
0.3% (n=3,521) at 1-year
0.6% (n=5,802) at 2-years
1.1% (n=9,564) at 5 years

Total infections = 11,619 (1.1%)

18.1% (n=2,109)
extracted within
30-days

81.8% (n=9,510)
no extraction
within 30-days

Cumulative Mortality According to Timing of Extraction



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DCRI Demonstration Project for Improving Care of Device Infection: 3 U.S. Centers

Develop a model to increase guideline-driven care for patients with definitive or suspected CIED infection

1. Measure guideline adherence before and after interventions
2. Demonstrate a model of how to assemble interdisciplinary teams to address gaps in care for recognizing and treating CIED infection
3. Improve early identification and treatment of CIED infection with removal
4. Demonstrate institutional care pathways to improve guideline directed care

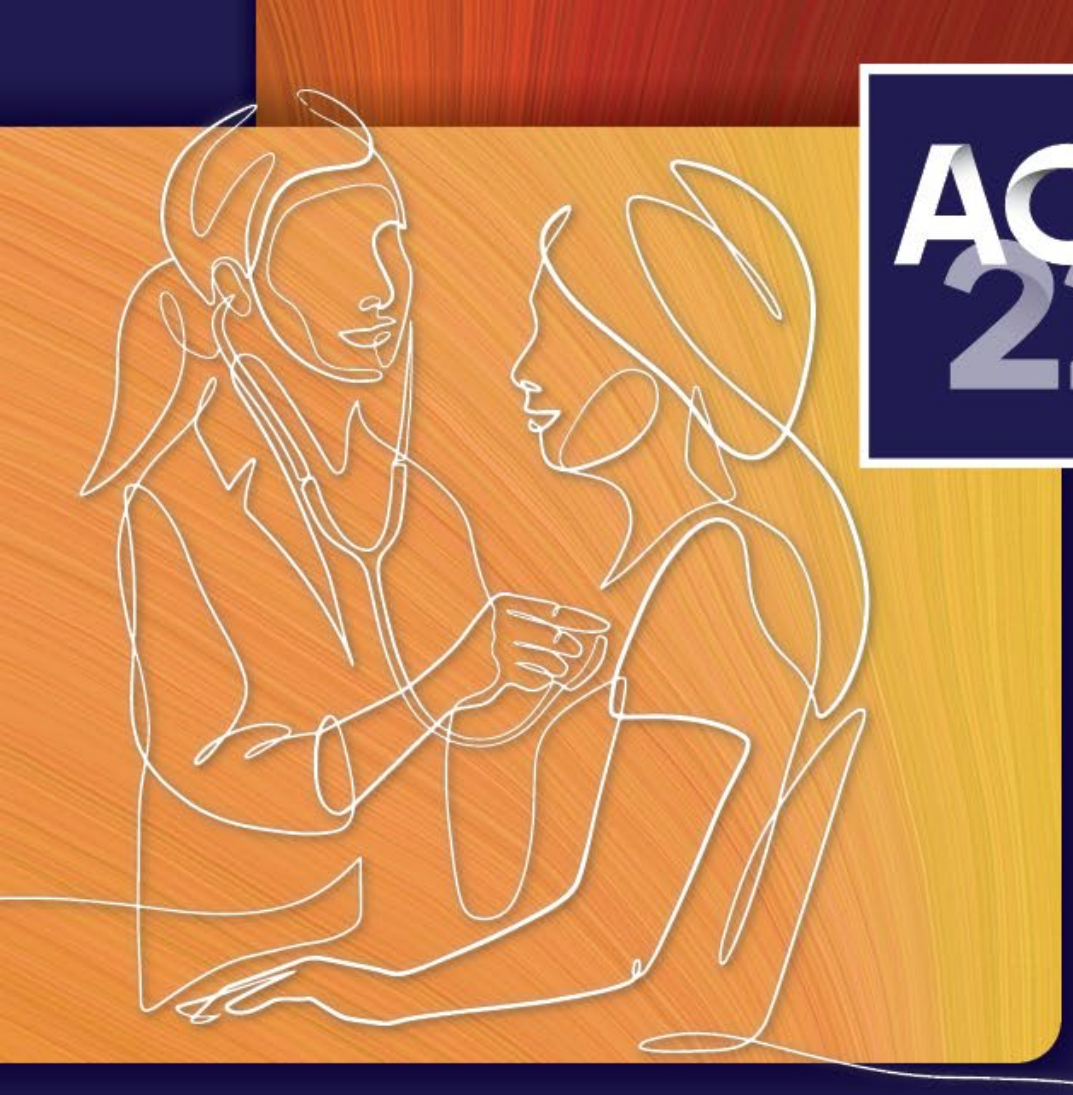
DCRI Demonstration Project for Improving Care of Device Infection: 3 U.S. Centers

The QI Program will include development and/or refinements of participating health system's patient care pathways **tailored** to meet the gaps and barriers (**multifaceted intervention**).

Interventions will be customized and modified as needed based on regular review of data (**data measurement and feedback**)

Establish **multidisciplinary team**, led by a committed clinician, with a Duke implementation team (**outreach visits**) to define gaps in care, monitor ongoing data, identify barriers to guideline-directed care, and develop and implement multifaceted intervention to address the barriers.

- Multidisciplinary team to include but not be limited to: EP extractor, hospital administration, ID, hospitalist, cardiologist, nursing educator, patient navigator/educator, patient, device clinic staff, quality specialist
- Aim for alignment of administrators, clinicians, patients
- Tools/specific interventions to include EMR alerts, device check forms, OR block time and dedicated surgical back-up, formal bimonthly review of data, surveys, care pathways, targeted education



ACC 22

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

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Consumer-led Screening For Atrial Fibrillation: A Report From The mAFA-II Trial Long-term Extension Cohort

Yutao Guo[1,2], Gregory Y.H. Lip[2],

on behalf of the mAF-App II Trial investigators

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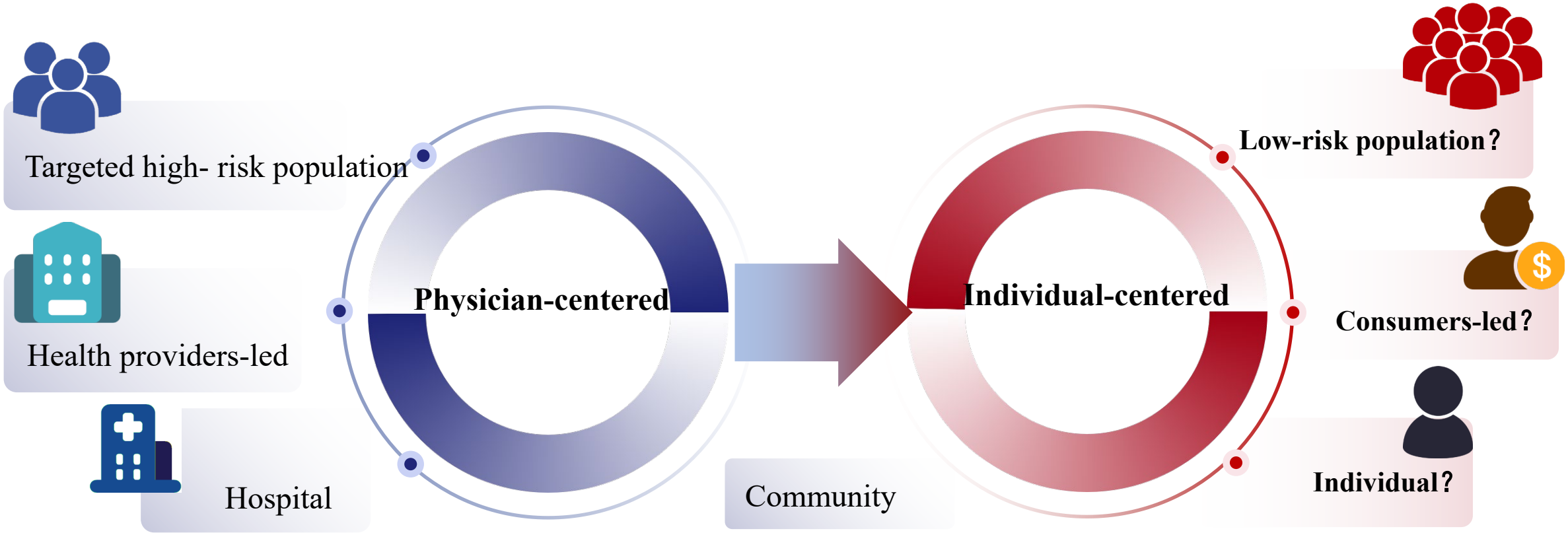
Disclosure

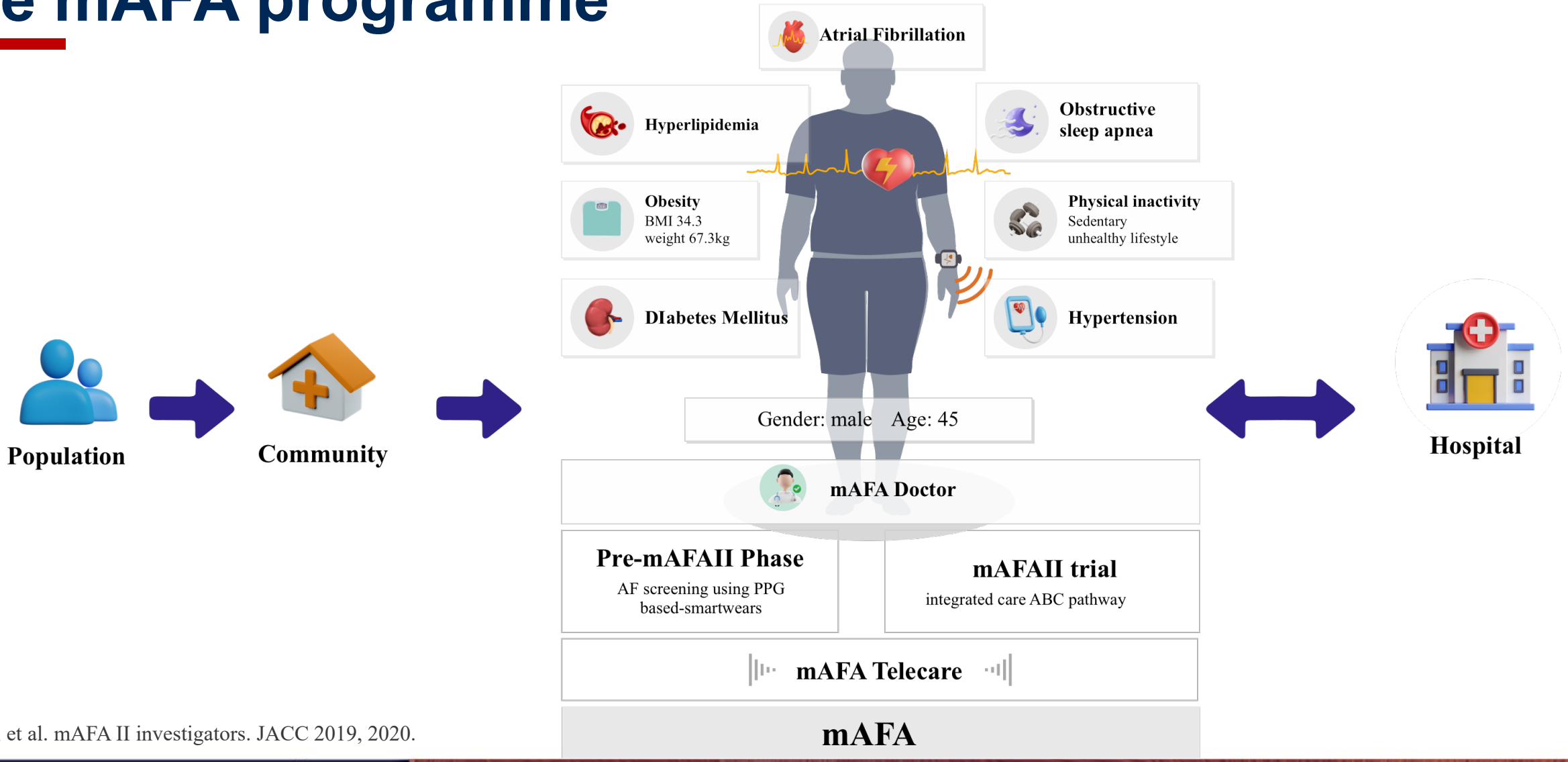
I have no declaration of interests related to this work.

Background



What would these bring out on the landscape of AF prevention and treatment?

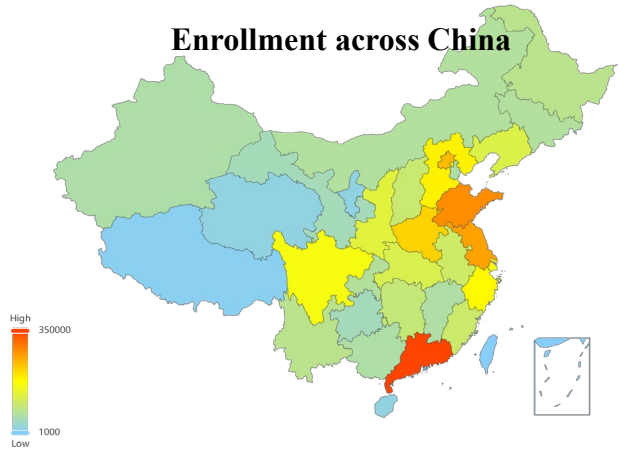
The mAFA programme

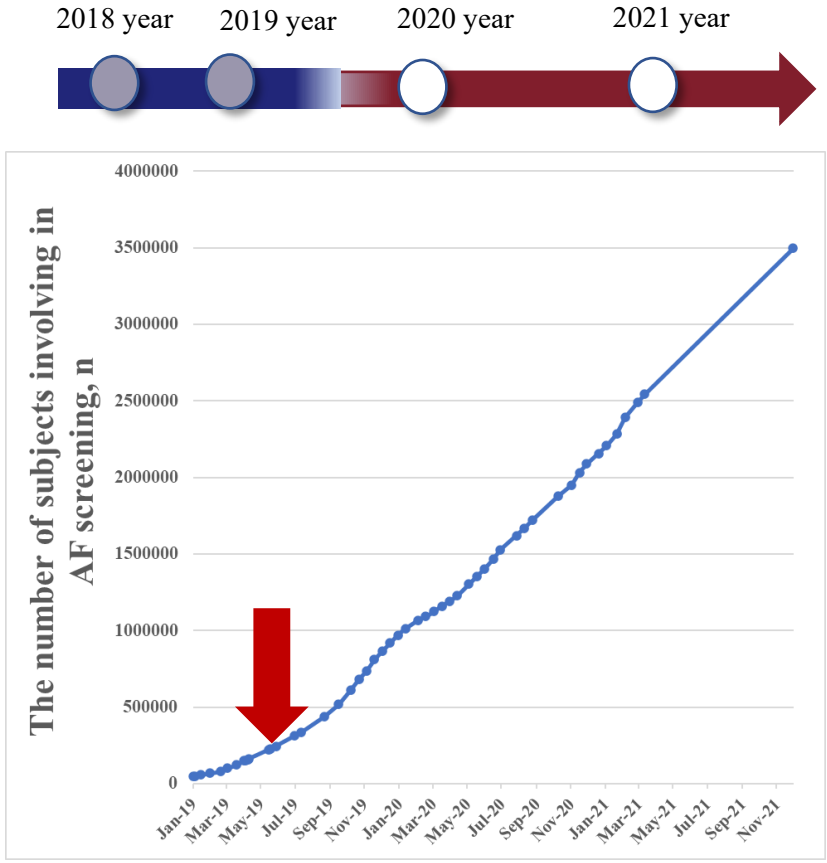


Guo Y, et al. mAFA II investigators. JACC 2019, 2020.

Objective

To describe trends on prevalent AF detection and risk factors in the general population over time with consumer-led mass population screening for AF





*** Red arrow means the end study date of reported Huawei Heart Study (Guo Y， et al. JACC. 2019).**

Methods

Pre-mAFA: AF screening

3 499 461 subjects downloaded Screening App across China (October 26, 2018 and Dec 1, 2021)

Inclusion
Adult ≥ 18 years
Huawei phone (Android 5.0 or higher)
Huawei & Honor smart devices

Exclusion
Adult < 18 years
Inability to use smart phone or devices

647 087 subjects without compatible devices excluded from analysis

2 852 374 subjects had rhythm monitoring data

157 subjects with unknown rhythm excluded

2 852 217 subjects into the final analysis

AF screening

12 244 (0.4%) subjects received the notification of **suspected AF**

2447 subjects refuse to be followed up

5227 (53.3%, 5227/9797) subjects effectively follow-up by mAFA Telecare Team and doctors

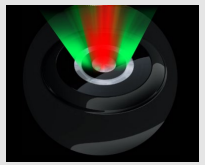
PPG algorithm for AF was validated compared to 12-lead ECGor 24-h holter
(Fan YY, et al.JMIR Mhealth Uhealth 2019; Zhang H, et al.J Med Internet Res 2019).

59 sinus rhythm
168 atrial/ventricle premature
74 other arrhythmia
23 unknown rhythm

4903 (93.8%, 4903/5227) subjects confirmed with the diagnosis of AF with clinical evaluation and 12-lead ECG, or 24-h ECG

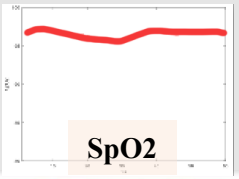
Obstructive sleep apnea screening

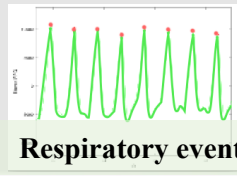
979 013 subjects screened both **AF and OSA risk**

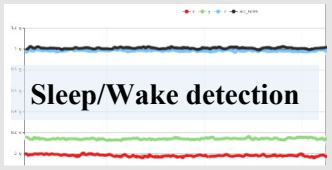


PPG algorithm for OSA risk was validated compared to polysomnography or home sleep apnea test
(Chen Y, et al.. Nat Sci Sleep 2021)

6120 subjects (0.6%, 6120/979 013) with detected AF episodes







Flow chart of consumer-led screening for AF

* mAFA: mobile Atrial Fibrillation Application. OSAS: Sleep apnea-hypopnea syndrome.

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- Compared to **12-lead ECG**, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of mobile phones with PPG for AF detection were over 94% (Fan YY, et al. JMIR Mhealth Uhealth. 2019) .
- Compared **to home sleep apnea test**, the PPG algorithm based on smart devices detected moderate-to-severe OSA patients (apnea hypopnea index, AHI ≥ 15), with the accuracy, sensitivity, and specificity of 87.9%, 89.7% , and 86.0%, respectively. Compared to **polysomnography**, the accuracy, sensitivity, and specificity of the PPG-based smartwatch in predicting OSA in patients (AHI≥5) were 81.1%, 76.5%, and 100%, respectively. (Chen Y, et al. Nat Sci Sleep 2021) .

Statistical Analyses

A Cox proportional hazards model was utilised to analyze the association of enrolled year and detected AF episodes, after adjustment (for age, gender, area, palpitation symptoms, hypertension, diabetes, sleep apnea, CAD, hyperthyroidism, and heart failure) and adjusted hazard ratios (hazard ratio, HR, 95% confidential interval, CI) are presented.

A logistic multivariate regression analysis was used to assess the effects of risk strata of sleep apnea on the detected prevalent AF episodes, among subjects simultaneously received sleep apnea screening and AF screening using the AF screening App.

Results

Table Baseline characteristics of 2 852 217 subjects with smart devices between 2018-2021

	Oct 26, 2018-Dec 31, 2018 (n=25 782)	Jan 1, 2019-Dec 31, 2019 (n=751 341)	Jan 1, 2020-Dec 31, 2020 (n=1 040 043)	Jan 1, 2021-Dec 1, 2021 (n=1 035 051)
Age, mean ± SD	37±17	36±22	38±13	38±12
Male, n (%)	23 407 (90.8%)	624 974 (83.2%)	847 394 (81.5%)	833 062 (80.5%)
User-reported risk profiles (n=1 314 964)	2018 (n=11 738)	2019 (n=331 909)	2020 (n=522 171)	2021 (n=449 146)
Palpitation, n (%)	3298 (28.1%)	101 482 (30.6%)	156 839 (30.0%)	134 979 (30.1%)
OSA, n (%)	3763 (32.1%)	111 064 (33.5%)	172 010 (32.9%)	144 982 (32.3%)
Hypertension, n (%)	1930 (16.4%)	52 771 (15.9%)	87 022 (16.7%)	79 160 (17.6%)
Diabetes, n (%)	439(3.7%)	12 620(3.8%)	21 873 (4.2%)	20 714 (4.6%)
CAD, n (%)	362(3.1%)	9767(2.9%)	16 895 (3.2%)	16 059 (3.6%)
Heart failure, n (%)	161(1.4%)	5053 (1.5%)	8336 (1.6%)	7577 (1.7%)
Hyperthyroidism, n (%)	161 (1.4%)	4725 (1.4%)	7738 (1.5%)	6960 (1.5%)

* SD: standard deviation. OSA: obstructive sleep apnea syndrome. CAD: coronary artery disease.

Results

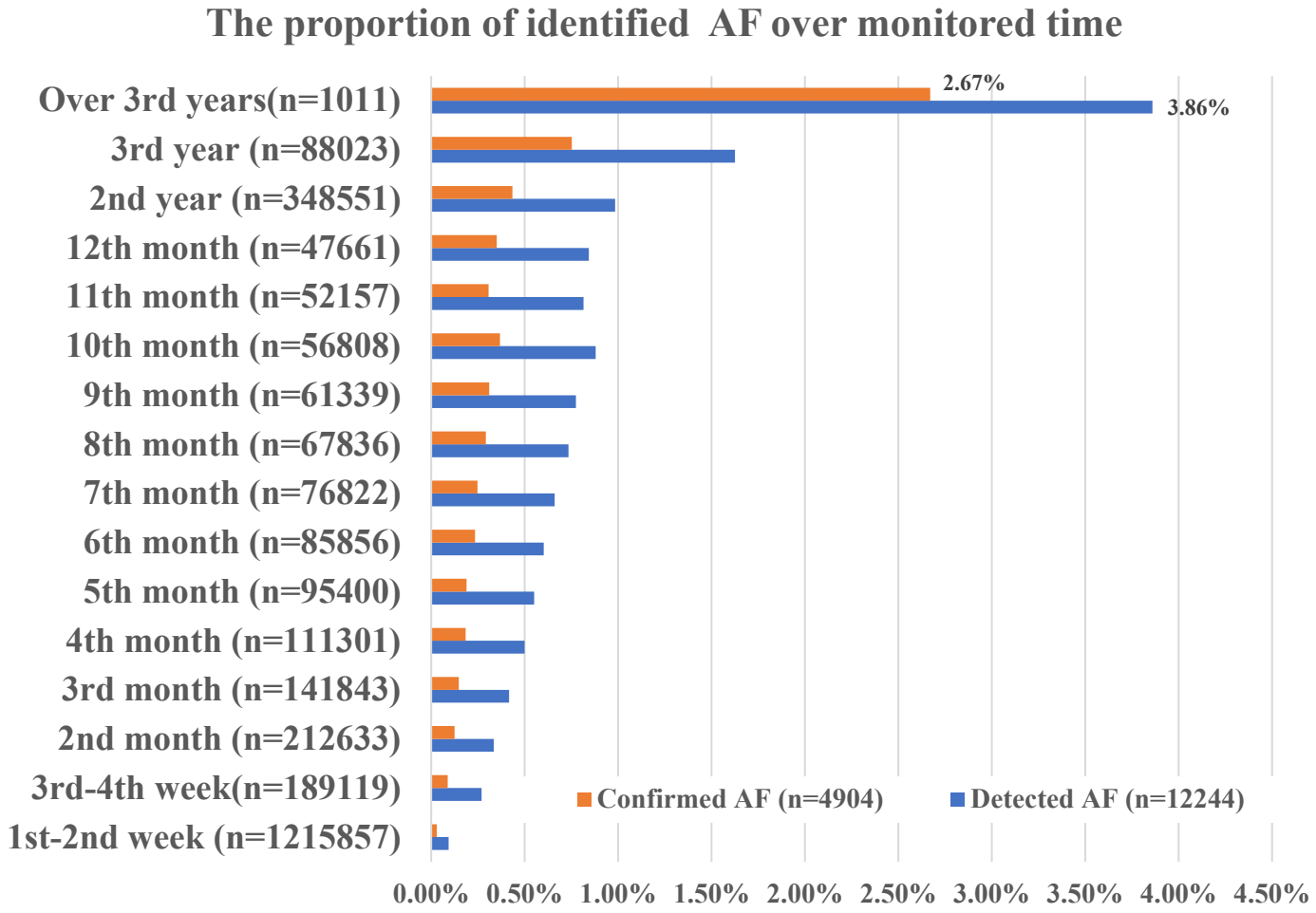
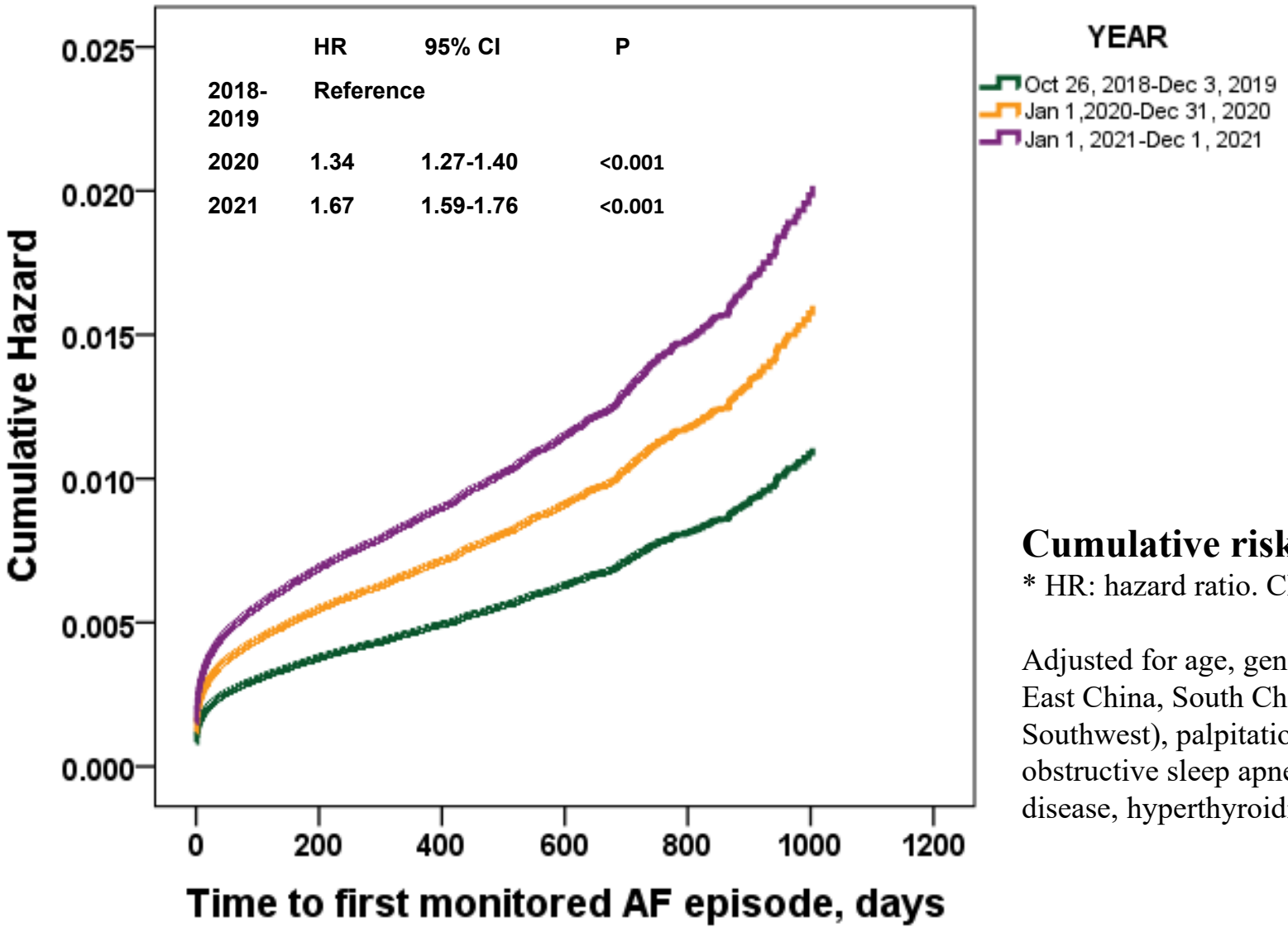


Figure 2 Proportion of suspected AF monitored by smart devices, in relation to the continuous monitoring time

* Monitoring time: the time from first measurement to the last measurement

Results

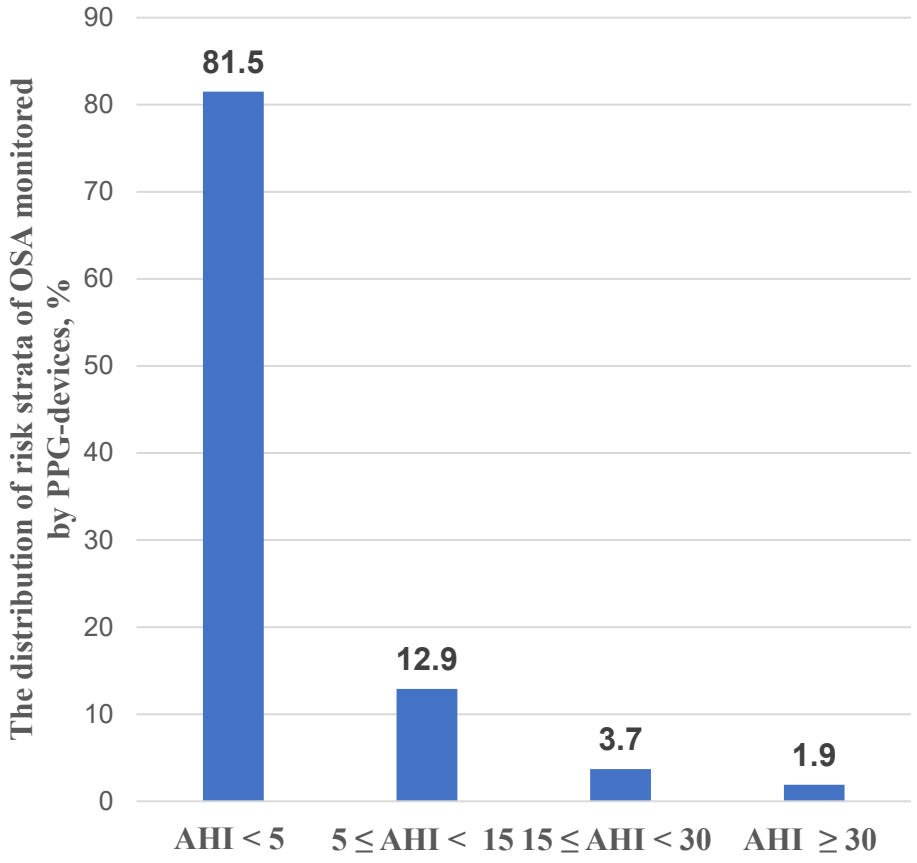


Cumulative risk of monitored AF

* HR: hazard ratio. CI: confidential interval.

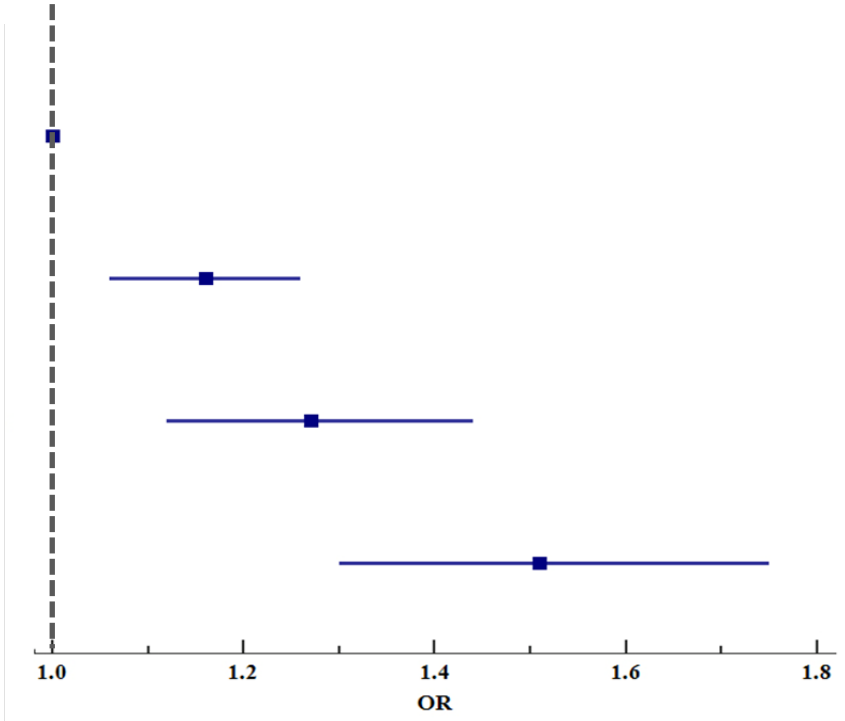
Adjusted for age, gender, area (Northeast, North China, East China, South China, Central China, Northwest, and Southwest), palpitation, hypertension, diabetes, obstructive sleep apnea syndrome, coronary artery disease, hyperthyroidism, and heart failure.

Results



The distribution of the risk of OSAS monitored by PPG algorithm (n=962 087)

Risk strata	OR (95%CI)	P
AHI < 5	Reference	
5 ≤ AHI < 15	1.16 (1.06-1.26)	< 0.001
15 ≤ AHI < 30	1.27 (1.12-1.44)	< 0.001
AHI ≥ 30	1.51 (1.30-1.75)	< 0 .001



Odd Ratios of prevalent AF detection, in relation to risk strata of OSA

OSA: Obstructive sleep apnea. AHI: apnea hypopnea index. OR: odd ratio. CI: confidential interval. There were 961 931 who received screening both for AF and OSA risk, and 6120 subjects were monitored with suspected AF.

- 'High-risk' of OSA: more than 80% monitoring measures with AHI ≥ 30 during sleep
- 'Intermediate-risk' OSA: more than 80% monitoring measures with 15 < AHI < 30 during sleep
- 'Low-risk' OSA: more than 80% monitoring measures with 5 < AHI ≤ 15 during sleep

Limitations

- Only 53.3% subjects with identified suspected AF were effectively followed up by mAFA Telecare Team and doctors.
  - Relatively 'low-risk' population with mean age of 37 years involving in 3.5 million subjects over three years, were less willing to have further confirmation, possibly because of their asymptomatic status.
  - Some AF episodes might be missed. Nonetheless, the increased prevalent AF observed over time by the devices.

- Given this was a large prospective consumer-led screening study, we cannot confirm that the first detected AF episode was a 'new' AF episode, or 'paroxysmal episode', or 'asymptomatic' AF.

Limitations

- The increased trend on prevalent incident suspected AF was similar to prevalent confirmed AF over monitoring time, that was, the more AF episodes the long the monitored time. It may reflect the real-world setting-----those who would like to monitor their pulse rhythm were more likely to have AF.

- The AF screening App is freely available in the AppStore, not only for the patients in the hospital.

Conclusions

- A consumer-led mass population AF screening approach can facilitate screening for AF with >93% confirmation of detected AF episodes, even for the low-risk general population, with more prolonged monitoring.
- A consumer-led screening approach demonstrates the increased risk for detecting prevalent AF episodes over time.

Over 90% confirmed AF detection was reported in population screening for 7 months (JACC. 2019)**, cohort over one year** (Eur J Intern Med.2020), **and current cohort over three year…**

Conclusions

- OSA (as detected by smartwear) was most reported common risk factors that increase AF susceptibility, while high-risk OSA (more than 80% monitoring measures with AHI $\geq$ 30 during sleep) resulted in a 1.5-fold increase in prevalent AF.

Consumer led screening could increase early diagnosis of AF and facilitate an integrated approach to fully implement clustered risk management to reduce AF burden and its-related complications…

Acknowledgments

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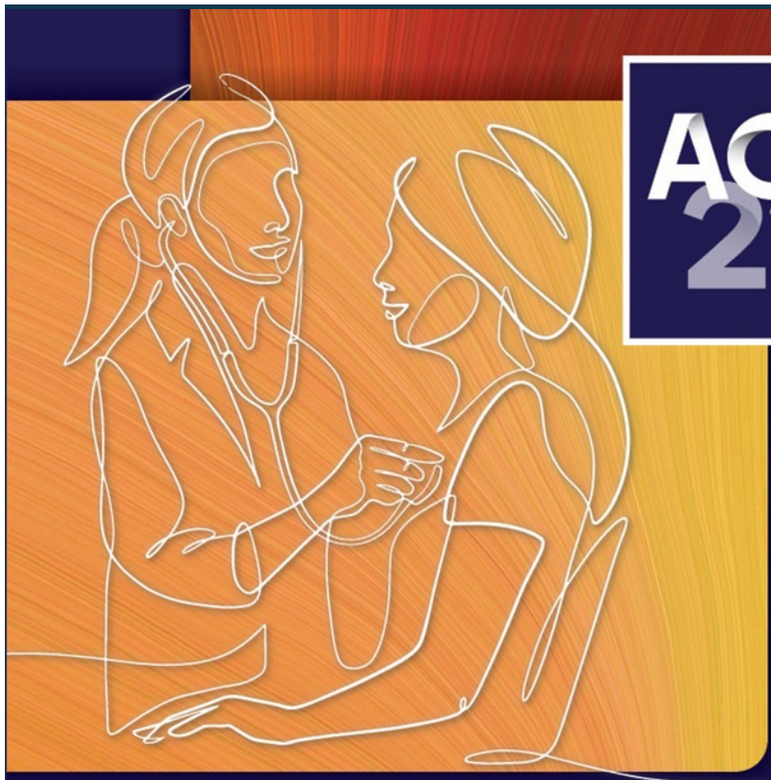
Sincere Thanks to the **HUAWEI Heart Health Research Team** for the smart technology support, headed by Mr. Xiaoxiang He.

Team members include Jiabing Yan, Wenjuan Chen, Qin Chen, Rong Sheng, Yumei Chen, Tiantian Qin, Yong Chen, Lian Wu, Xi Huang, Hongbao Li, Zhongjie Hou, Anqi Zhang , Zouzhen Wu, Lingzhi Qiu, JiaHui Peng, Maolin Chen, Shuai Zhao, Luping Li, Hao Xiong, Lingjie Liu, Jili Yuan, Jing Li

Thank you for your attention



Multicenter, Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation: PACIFIC-AF

Manesh R. Patel, MD on behalf of the PACIFIC-AF Investigators

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PACIFIC AF

Disclosures

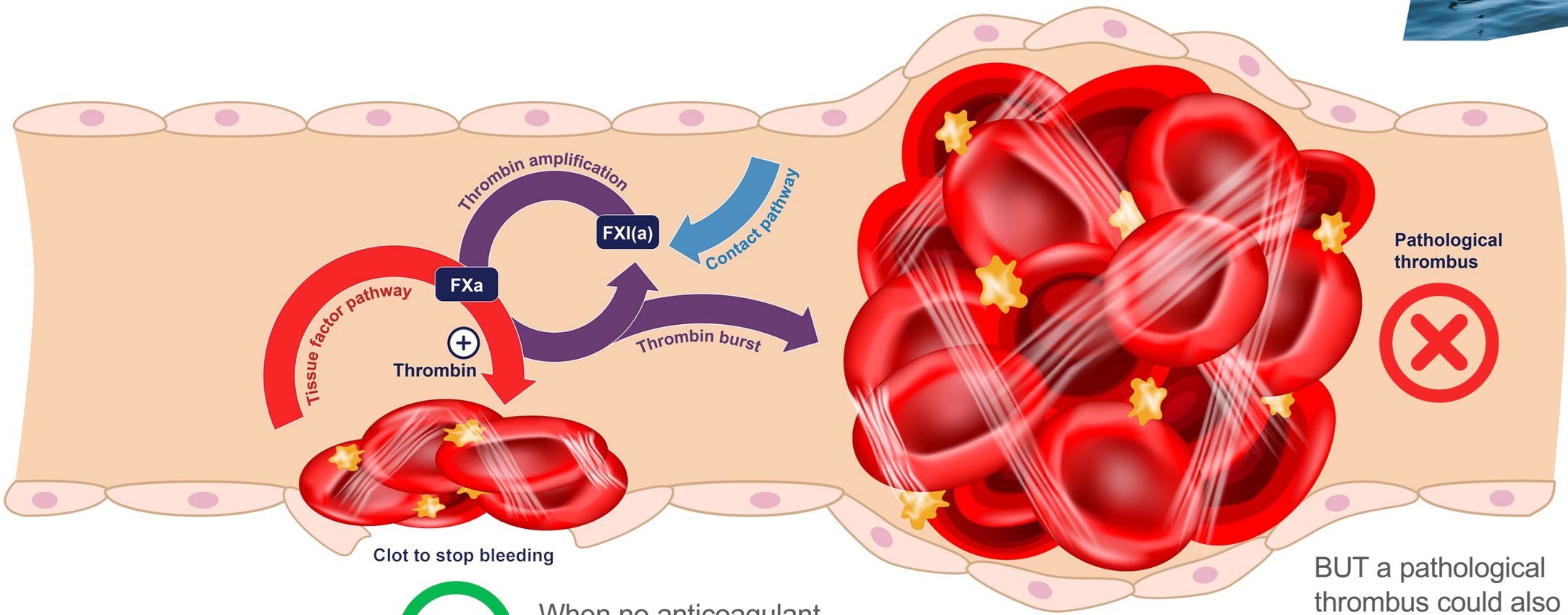
Research Grants:

PACIFIC-AF: Bayer

Other Research Support: Janssen, Heartflow, Idorsia, NHLBI, Novartis

Advisory Board/Consulting: Bayer, Janssen, Heartflow, Medscape

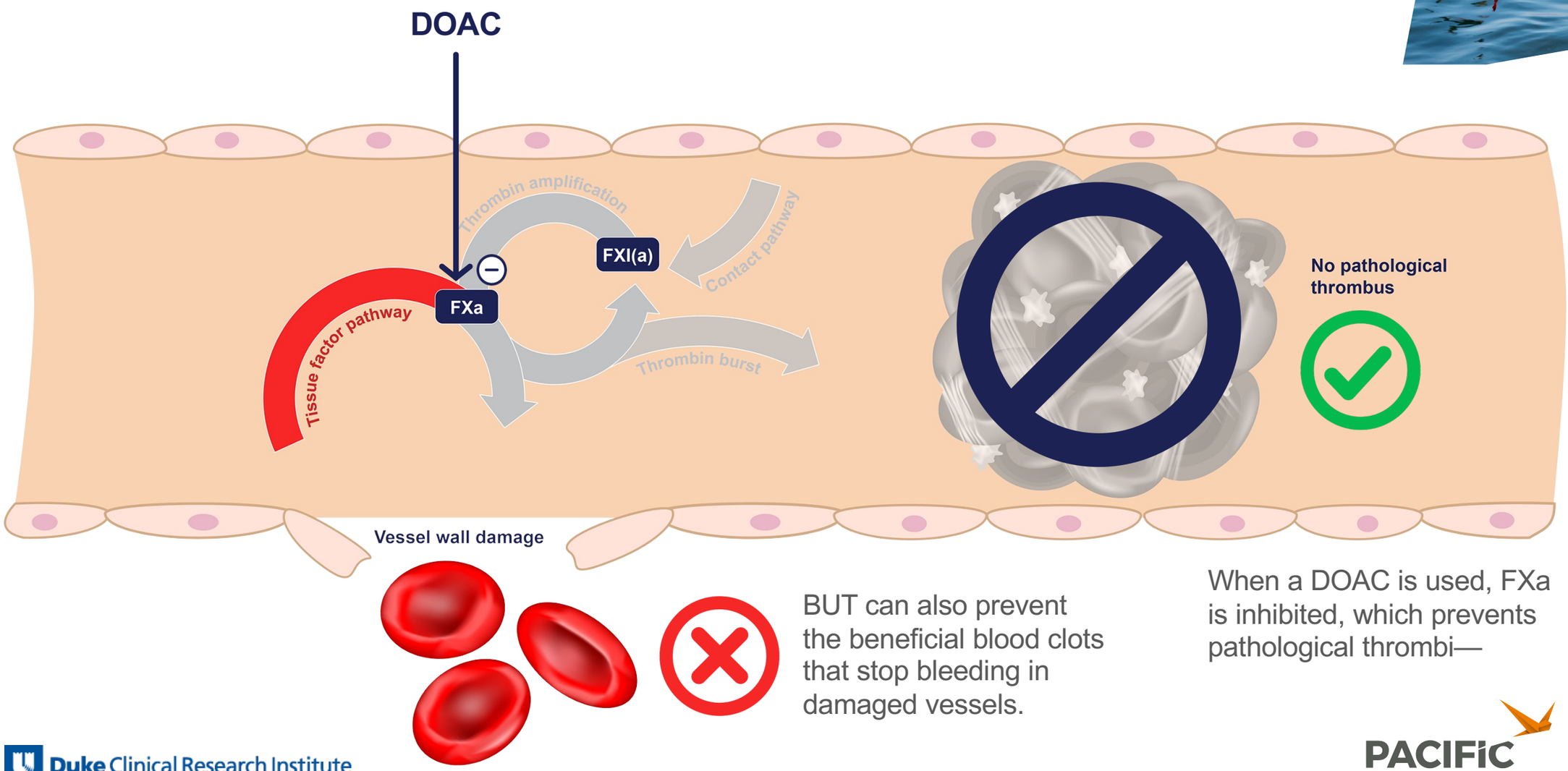
Normal Physiology: Without an Anticoagulant



When no anticoagulant is used, a clot is formed to stop the bleeding—

BUT a pathological thrombus could also be created.

With a DOAC (e.g., apixaban or rivaroxaban)



BUT can also prevent the beneficial blood clots that stop bleeding in damaged vessels.

When a DOAC is used, FXa is inhibited, which prevents pathological thrombi—

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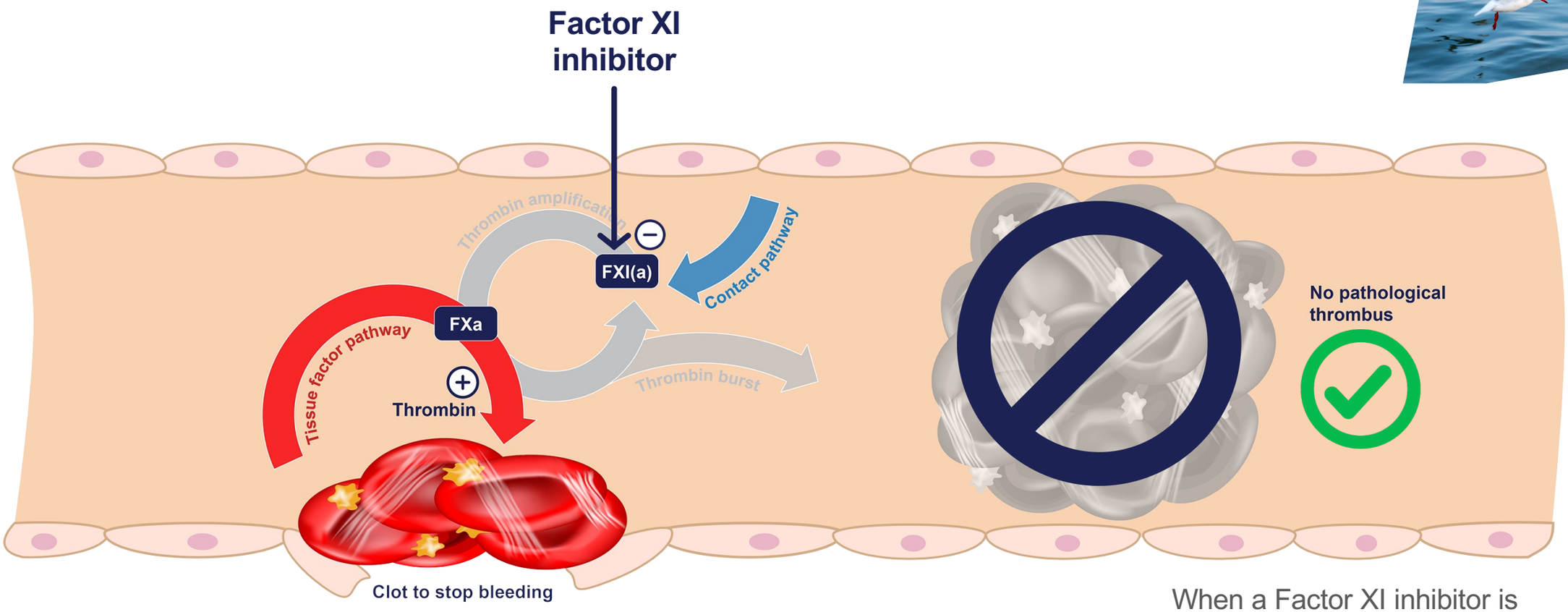
PACIFIC AF

With a Factor XI Inhibitor (Hypothesis: Uncoupling Hemostasis from Thrombosis)



AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form.

When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi—

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PACIFIC AF

Current Evidence Supporting FXI(a) Inhibition as a Target

CONDITION	OBSERVATION
FXI-knockout mice[1]	• Homozygous FXI-knockout mice **are protected from thrombosis** • At the same time, they **do not show a bleeding phenotype** differing from wild-type mice
***In vivo* animal models**[2]	• Reducing/inhibiting FXI showed **strong antithrombotic** effects *in vivo* • **No increase in bleeding time** even at very high doses or on top of dual antiplatelet therapy
Inherited FXI deficiency[3]	• Individuals with FXI deficiency are reported to have a **reduced incidence of VTE and stroke** • **Hemorrhage occasionally** reported after trauma or surgery (dental extractions, tonsillectomies, surgery in the urinary and genital tracts, and nasal surgery)
FXI clinical experience	• **Antisense technology of IONIS**[4]**: Phase 2 study in TKA**: Improved VTE risk reduction together with numerically less bleeding vs enoxaparin (**of note, surgery was performed at suppressed FXI levels**) • **Anti-FXI-AB** (MAA868[5] and xisomab); **Anti-FXIa-AB** (osocimab[2]): Published data from Phase 1 studies confirmed **good safety and tolerability** even when high levels of **FXI or FXIa inhibition** were maintained for more than **1 month**. TKA study for osocimab completed confirming FXIa-inhibition being efficacious and well tolerated. **Oral selective FXIa inhibitor** (milvexian): Phase 2 work showing FXIa inhibition efficacious in **prevention of VTE** and associated with **low risk of bleeding**.[6]

[1] Schumacher WA et al. Arterioscler Thromb Vasc Biol. 2010;30(3):388-92.
[2] Data on file
[3] Puy C et al. Thromb Res. 2016;141(Suppl 2):S8–S11
[4] Büller HR et al. N Engl J Med. 2015;372(3):232-40
[5] Koch AW et al. Blood. 2019;133(13):1507-1516
[6] Weitz et al. N Engl J Med. 2021;385(23):2161-2172

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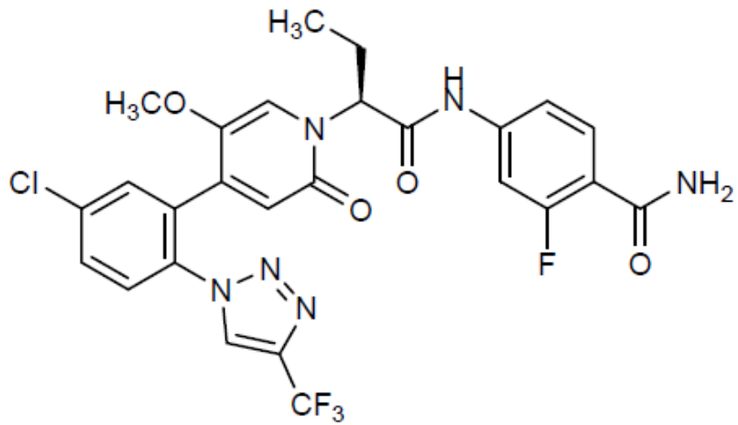
PACIFIC AF

Asundexian: Oral Factor XI Inhibitor

$C_{26}H_{21}ClF_4N_6O_4$



- Small molecule FXIa inhibitor
  - $t_{1/2}$ 14.2-17.4 hours
  - 15% Renal Elimination
- Well-tolerated in Phase 1 trials
- Dose-dependent FXIa inhibition
- Does not interact with clopidogrel to affect bleeding time
- No difference across age or sex
- Does not inhibit or induce CYP3A4
- Not impacted by food or pH modulating drugs

The PACIFIC Trials: Coordinated Phase 2 Programs

- Together, will allow to assess the bleeding and efficacy profile of asundexian
- **Primary objective of PACIFIC-AF: evaluate comparative bleeding rate of asundexian vs apixaban in patients with AF**
- No assessment of efficacy possible given low event #
- PACIFIC-AMI and PACIFIC-STROKE as placebo-controlled studies on top of antiplatelet therapy
- PACIFIC-AF is the first Phase 2 study that will read out

PACIFIC AF

PACIFIC AMI

PACIFIC STROKE

PACIFIC Program

Concerted evaluation across large several Phase 2 programs

PACIFIC AF

Atrial fibrillation

20mg asundexian
50mg asundexian
apixaban

750 patients randomized
Results at ACC 2022

PACIFIC STROKE

Non-cardioembolic ischemic stroke

10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ single or dual antiplatelet therapy

1800 patients randomized
Results later this year

PACIFIC AMI

Acute myocardial infarction

10mg asundexian
20mg asundexian
50mg asundexian
placebo

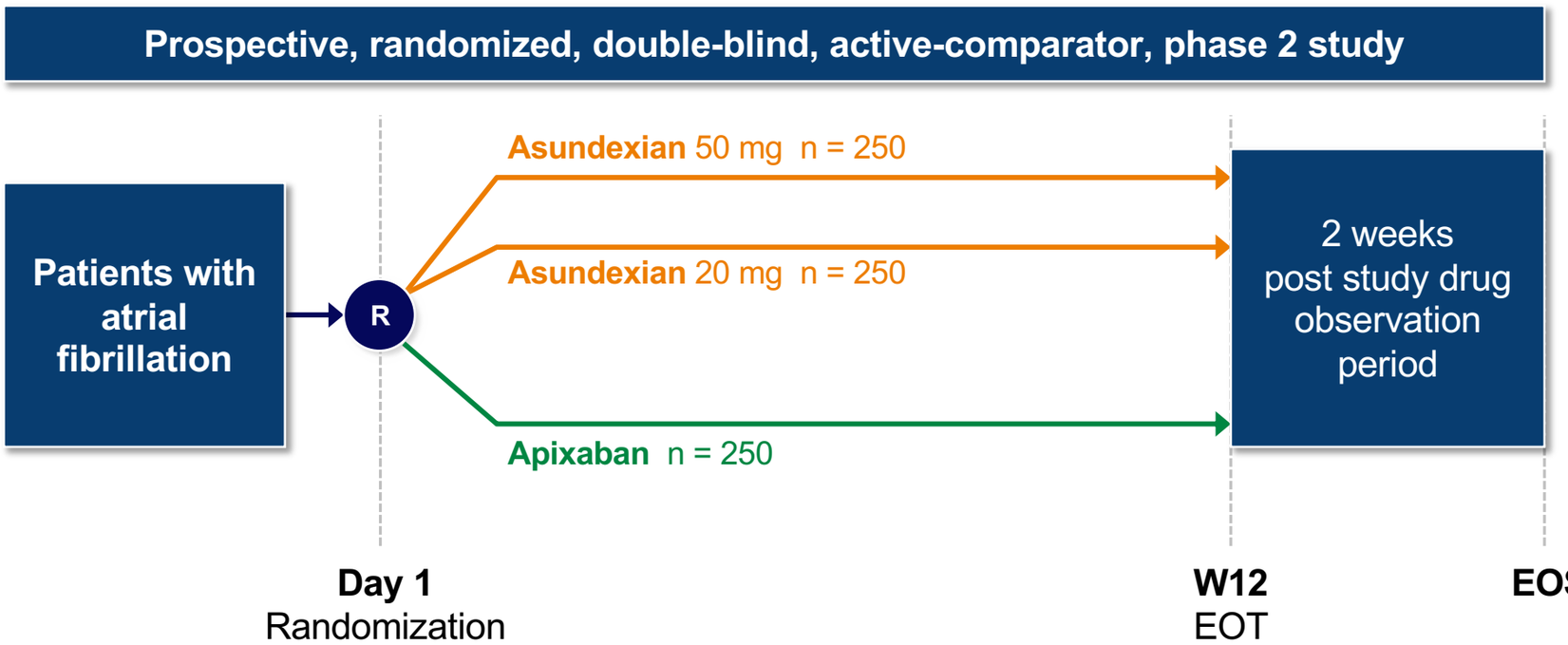
+ dual antiplatelet therapy

1600 patients randomized
Results later this year

// One coordinated IDMC

// One blinded CEC with uniform process

Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study to Compare the Safety of the Oral FXIa Inhibitor Asundexian to Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF)



Primary safety endpoint: bleeding (ISTH major and non-major clinically relevant bleeding)

Quantification of Factor XI inhibition

Exploratory efficacy endpoint: stroke, systemic embolism, CV death, MI

Primary Objective:
to evaluate that the oral FXIa inhibitor asundexian when compared to apixaban leads to a **lower incidence of bleeding** in participants with AF

PACIFIC AF

AXIA: Factor XIa Inhibition Assay

- Proprietary assay
- ~220 patients/ arm
- 4 weeks on once daily drug
- ~ trough (24-28 hours from last dose) and then again 2-4 hours afterwards
- Quantify degree of Factor XIa inhibition

Results of PACFIC-AF

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Disposition / Study Flow

Enrolled
862

Randomized (FAS)
755

Treatment Phase started (SAF)
753

Treatment Phase completed
671

Screening failures 107

Inclusion/exclusion criteria 69
Withdrawal by subject 28
Other reasons 10

Never took any study drug 2

Did not complete treatment phase 82

Adverse event 38
Other reasons 25
Death 6
Physician decision 6
Withdrawal by subject 6
Non-compliance with study drug 1

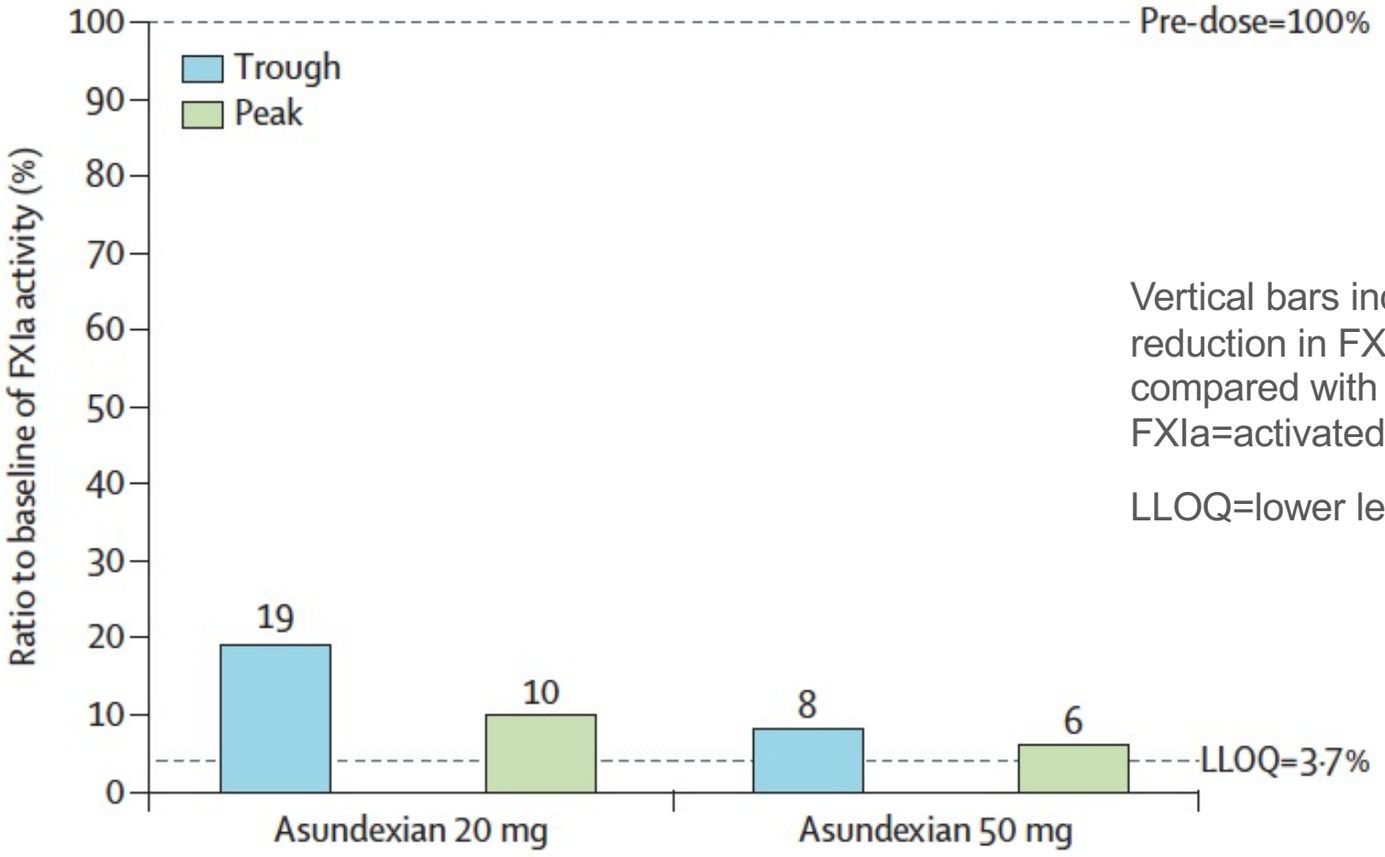
Demographics and Medical History — Well Balanced Across Treatment Arms

	Asundexian 20 mg N = 251	Asundexian 50 mg N = 254	Apixaban N = 250	Total N = 755
Age (years) (SD)	73.6 (8.0)	73.1 (8.5)	74.3 (8.3)	**73.7 (8.3)**
Female	103 (41.0%)	97 (38.2%)	109 (43.6%)	**309 (40.9%)**
Race				
White	211 (84.1%)	212 (83.5%)	209 (83.6%)	**632 (83.7%)**
Asian	39 (15.5%)	40 (15.7%)	40 (16.0%)	**119 (15.8%)**
Hypertension	226 (90.0%)	227 (89.4%)	220 (88.0%)	**673 (89.1%)**
Hyperlipidaemia	142 (56.6%)	153 (60.2%)	152 (60.8%)	**447 (59.2%)**
Cardiac failure chronic	108 (43.0%)	107 (42.1%)	117 (46.8%)	**332 (44.0%)**
Coronary artery disease	76 (30.3%)	71 (28.0%)	85 (34.0%)	**232 (30.7%)**
Diabetes mellitus	83 (33.1%)	74 (29.1%)	87 (34.8%)	**244 (32.3%)**
Chronic kidney disease	55 (21.9%)	84 (33.1%)	77 (30.8%)	**216 (28.6%)**
CHA_2DS_2-VASc score (SD)	3.99 (1.39)	3.83 (1.29)	4.10 (1.46)	**3.97 (1.38)**

Medical History of Special Interest

	Asundexian 20 mg N = 251	Asundexian 50 mg N = 254	Apixaban N = 250	Total N = 755
Cerebrovascular accident	22 (8.8%)	18 (7.1%)	25 (10.0%)	**65 (8.6%)**
Coronary artery bypass	22 (8.8%)	16 (6.3%)	17 (6.8%)	**55 (7.3%)**
Peripheral arterial occlusive disease	16 (6.4%)	10 (3.9%)	20 (8.0%)	**46 (6.1%)**
Transient ischemic attack	13 (5.2%)	10 (3.9%)	13 (5.2%)	**36 (4.8%)**
Major bleed	7 (2.8%)	14 (5.5%)	3 (1.2%)	**24 (3.2%)**
Carotid revascularization	3 (1.2%)	2 (0.8%)	4 (1.6%)	**9 (1.2%)**
Embolism arterial	3 (1.2%)	2 (0.8%)	2 (0.8%)	**7 (0.9%)**

FXIa Activity - Inhibition Data



	Asundexian 20 mg		Asundexian 50 mg	
n	224	222	228	228
Analysis value (95% CI)	14·82 (12·65–16·99)	7·42 (6·33–8·51)	6·59 (5·15–8·02)	4·32 (3·60–5·05)
Mean ratio to baseline (95% CI)	0·19 (0·16–0·22)	0·10 (0·08–0·12)	0·08 (0·07–0·10)	0·06 (0·05–0·07)

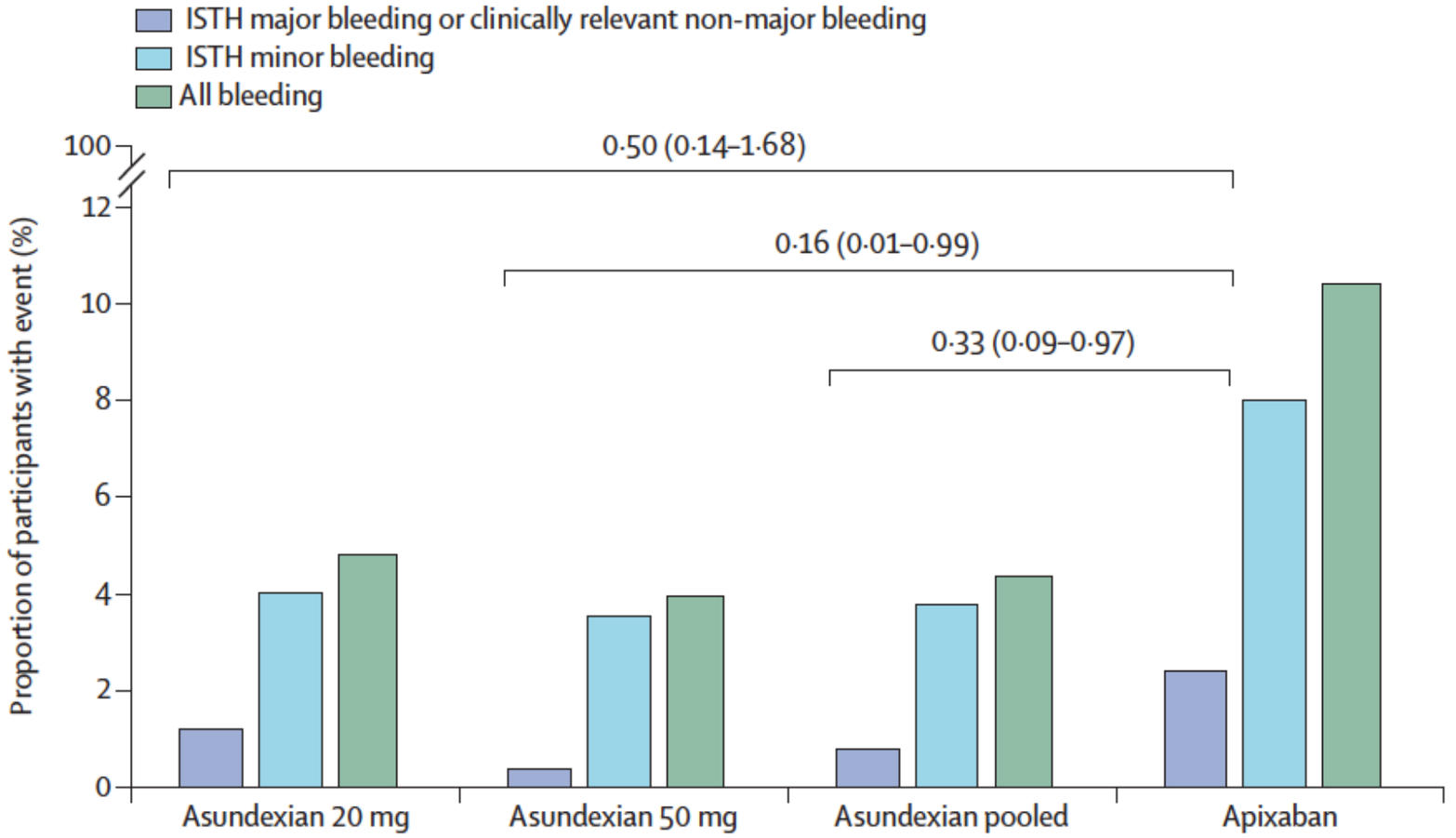
Vertical bars indicate the percent reduction in FXIa activity when compared with baseline.
FXIa=activated coagulation factor XI.

LLOQ=lower level of quantification.

PACIFIC AF

Primary Safety Outcome (ISTH bleeding classification)

On-treatment analysis, % of patients



- No ISTH **major** bleeding in any treatment arm
- Less bleeding in the 2 asundexian arms reported, when compared to apixaban for different severities of bleeding
- Consistent also for BARC and TIMI bleeding definitions

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PACIFIC AF

Primary Safety

(Pooled) ratio of the incidence proportions for the safety outcome in the treatment emergent data scope

	Asundexian 20 mg vs. Apixaban CIR (90% CI)	**Asundexian 50 mg vs. Apixaban** CIR (90% CI)	**Asundexian (pooled) vs. Apixaban** CIR (90% CI)
ISTH major bleeding or CRNM bleeding	0.50 (0.14 - 1.68)	0.16 (0.01 - 0.99)	0.33 (0.09 - **0.97**)
ISTH major bleeding	n.c.	n.c.	n.c.
CRNM bleeding	0.50 (0.14 - 1.68)	0.16 (0.01 - 0.99)	0.33 (0.09 - **0.97)**
ISTH minor bleeding	0.50 (0.23 - 0.99)	0.44 (0.18 - 0.86)	0.47 (0.28 - **0.83)**
All bleeding	0.46 (0.23 - 0.83)	0.38 (0.16 - 0.68)	0.42 (0.26 - **0.67)**

Adverse Events

	Asundexian 20 mg N = 249 (100%)	Asundexian 50 mg N = 254 (100%)	Apixaban N = 250 (100%)	Asundexian Total N = 503 (100%)	Total N = 753 (100%)
Any AE	118 (47.4%)	120 (47.2%)	122 (48.8%)	238 (47.3%)	360 (47.8%)
Any study drug-related AE	29 (11.6%)	26 (10.2%)	37 (14.8%)	55 (10.9%)	92 (12.2%)
Any AE leading to discontinuation of study drug	15 (6.0%)	16 (6.3%)	13 (5.2%)	31 (6.2%)	44 (5.8%)
Any study drug-related SAE	4 (1.6%)	0	0	4 (0.8%)	4 (0.5%)
AE with outcome death	1 (0.4%)	3 (1.2%)	2 (0.8%)	4 (0.8%)	6 (0.8%)

Asundexian was well tolerated in patients with AF.

Exploratory Efficacy Analysis

	Asundexian 20 mg N = 251 IR (90% CI)	**Asundexian 50 mg** N = 254 IR (90% CI)	**Apixaban** N = 250 IR (90% CI)	**Total** N = 755 IR (90% CI)
CV death, MI, ischemic stroke, or systemic embolism	2 (0.80 %)	4 (1.57 %)	3 (1.20 %)	9 (1.19 %)
CV death	1 (0.40 %)	3 (1.18 %)	3 (1.20 %)	7 (0.93 %)
MI	0	1 (0.39 %)	0	1 (0.13 %)
Ischemic stroke	2 (0.80 %)	1 (0.39 %)	0	3 (0.40 %)
Systemic embolism	0	0	0	0
All cause mortality (ITT)	2 (0.80 %)	4 (1.57 %)	4 (1.60 %)	10 (1.32 %)

As expected only single efficacy endpoints were reported in the study.

→ No conclusion on efficacy can be drawn

Summary

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Summary of Findings

- First randomized active comparator (apixaban) data with small molecule Factor XIa inhibitor (asundexian)
- Near complete inhibition of Factor XI activity with 20 and 50 mg dose asundexian
- Only few bleeding outcome events were observed
  - 48 participants with a bleeding event in total
- Point estimators of risk ratios in favor of asundexian
  - For the pooled 20 and 50 mg doses as well as for 50 mg alone the confidence intervals could exclude 1 for CRNM bleeding as well as for minor bleeding and all bleeding
  - Overall bleeding rates lower than expected (for Apixaban: 4% assumed vs. 2.4% observed)
- As expected — no information on efficacy events: limited events with fewer than 10 events total

Conclusions

- Asundexian, a small oral FXIa inhibitor was well tolerated in a Phase 2 trial of 750 patients with atrial fibrillation
- Significantly lower bleeding rates were seen for patients randomized to either dose asundexian compared to apixaban
- Factor XI inhibition is a promising strategy to prevent pathologic thrombi while minimizing bleeding risk in AF patients — Phase 3 trial required

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

*Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators**

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PACIFIC AF

Next Steps:
Engaging Patients and International Communities to Perform Clinical CV Outcomes Trial

- Net clinical benefit endpoints in upcoming OCEANIC AF trial will be informed by patient preference survey
- AFIBOPPORTUNITIES.COM
- Live Spring, 2022
- Engaging investigators who want to be part of innovative patient-centered trials (manesh.patel@duke.edu)

PEARL AF

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PACIFIC AF

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Hans Rickli
Laurent M. Haegeli
Angelo Auricchio
François Mach
Joris de Groot
Dominik Linz
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Louis Bartels
Ron Pisters
Aaf Kuijper
Ewout van den Bos
Jeroen Stevenhagen
Gregory Lip
Anthony Gunstone
Diana Gorog
Roxy Senior
Yuk-Ki Wong

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Thank you!

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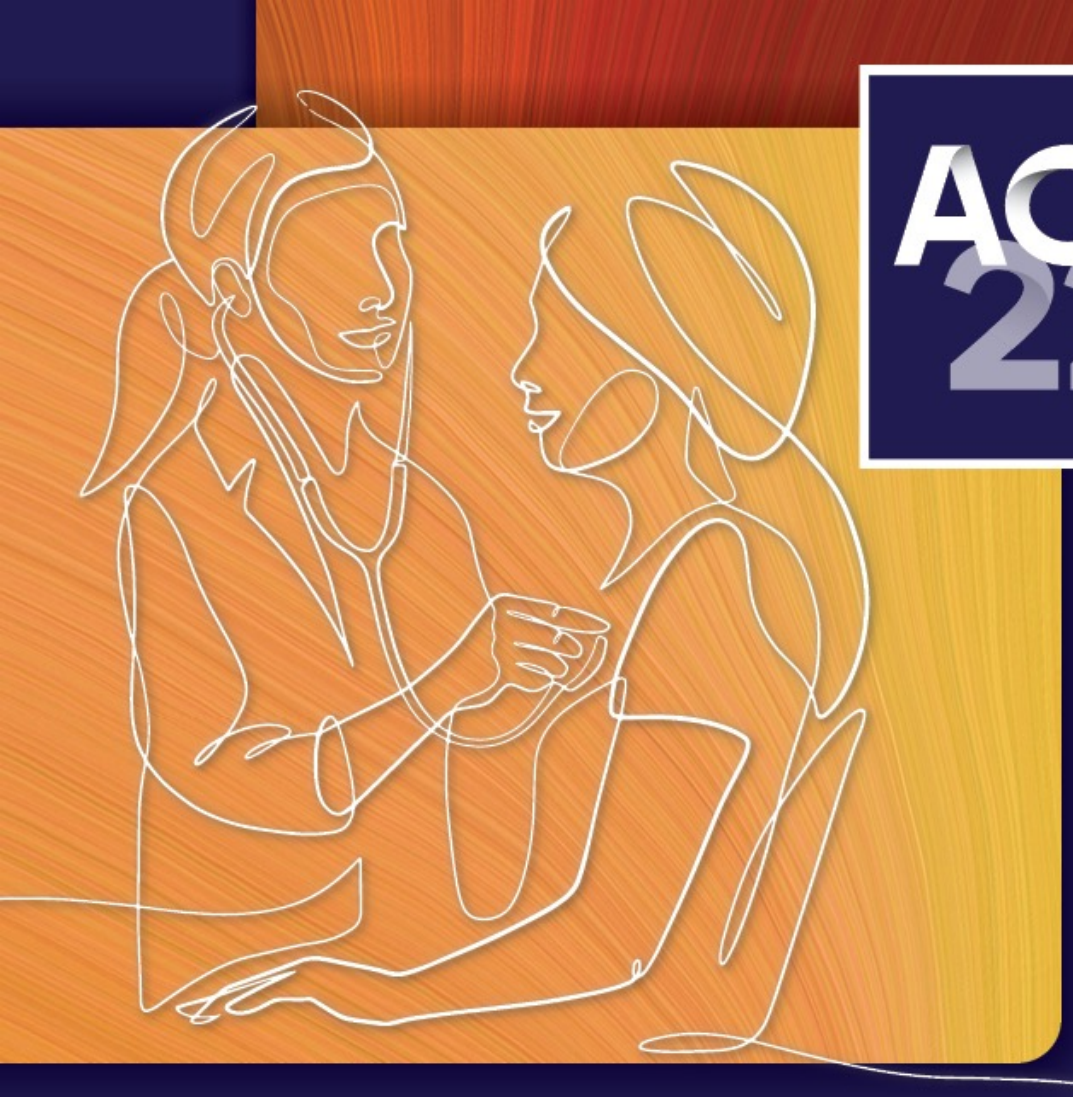

ACC 22

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Clinical Impact of Residual Leaks Following Left Atrial Appendage Occlusion: Insights from LAAO Registry

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Disclosures

The study was funded by a grant from Boston Scientific.

The sponsor had no role in the design of the study or the interpretation of the data

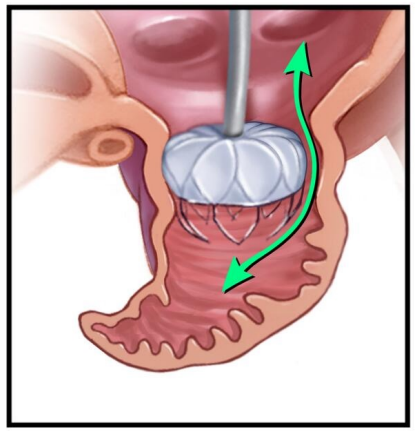
Left Atrial Appendage Occlusion; a Misnomer?

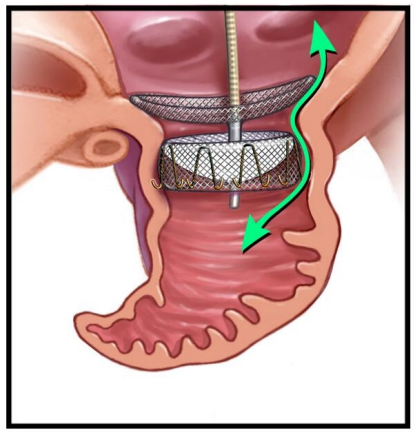
PROTECT AF [1]
- ❑ Any Leak: 40.9% at 45 day (32.1% at 1 year)
- ❑ Large (>3mm) leak: 13.3% at 45 day (11.8% at 1 year)

ACP Registry [2]
- ❑ Any leak: 12.5% at median f/u 134 days

PINNACLE FLX Trial [3]
- ❑ Any Leak: 7.4% at 45 day (10.5% at 1 year)
- ❑ Large (>5mm) leak: 0%

AMULET IDE Trial [4]
- ❑ Any Leak: 50.8% Watchman; 35.8% Amulet
- ❑ Large (>5mm) leak: 3.2% Watchman; 1.1% Amulet





[1] Viles-Gonzalez et al. JACC 2012;59:923–9
[2] Saw et al. JACC Intv 2017;10:391–9
[3] Kar et al. Circulation. 2021:4;143(18):1754-1762
[4] Lakkireddy et al. Circulation. 2021:9;144(19):1543-1552

Residual leaks after LAAO; Do They Matter?

PROTECT AF [1]

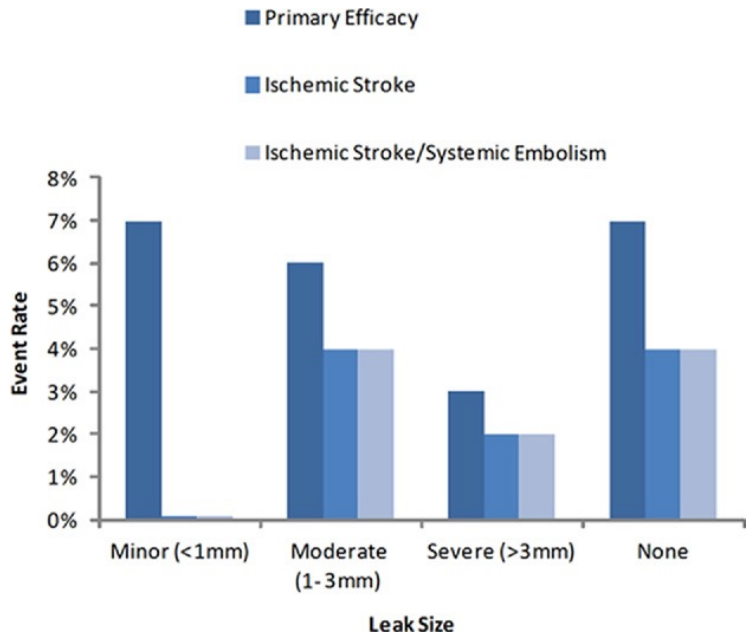
- ❑ No association with thromboembolic events (n=16)

ACP Registry [2]

- ❑ No association with thromboembolic events (n=7)

Vanderbilt Registry [3]

- ❑ The combined endpoint (failure to stop OAC, TIA or stroke, DRT, need for leak closure) was higher in patients with leaks >3 mm 69% vs 34%; p=0.002



[1] Viles-Gonzalez et al. JACC 2012;59:923–9
[2] Saw et al. JACC Intv 2017;10:391–9
[3] Afzal et al. JACC Clin Electrophysiol .2022;8(1):15-25.

Residual leaks after LAAO: Insights from NCDR

Study Design

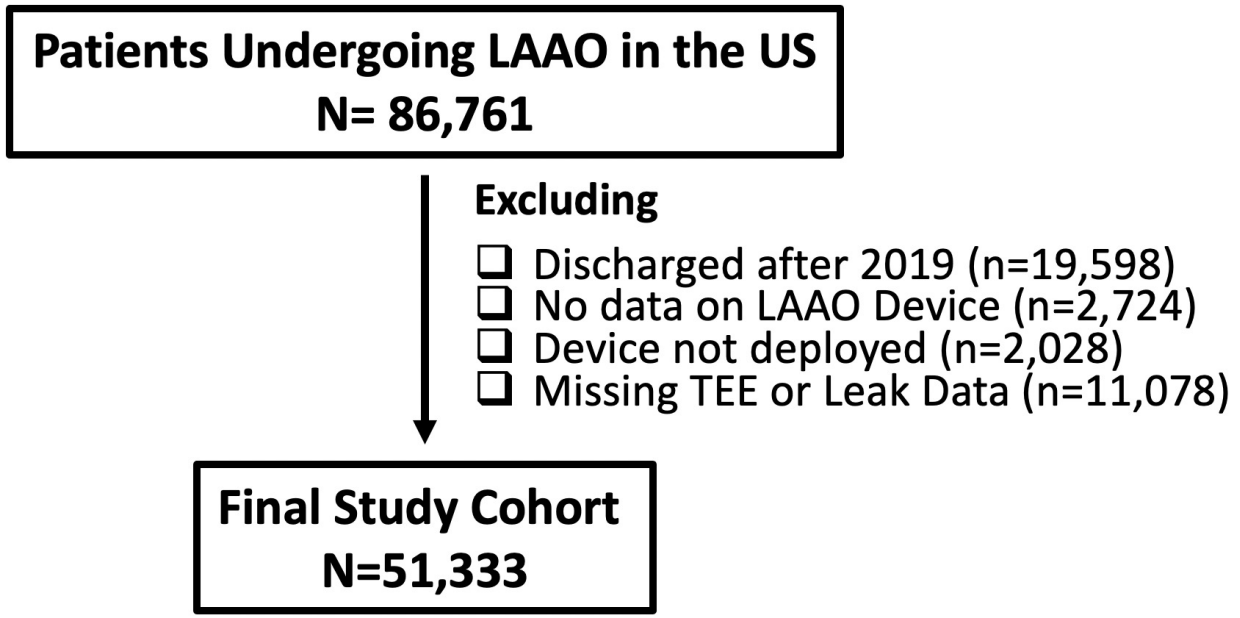
LAAO Registry

Inception & Timeline

- ❑ January 2016 – Registry Launched
- ❑ February 2016 - CMS NCD
- ❑ April 2016 – Mandate to Submit to LAAO

Data Collection & Utilization Process

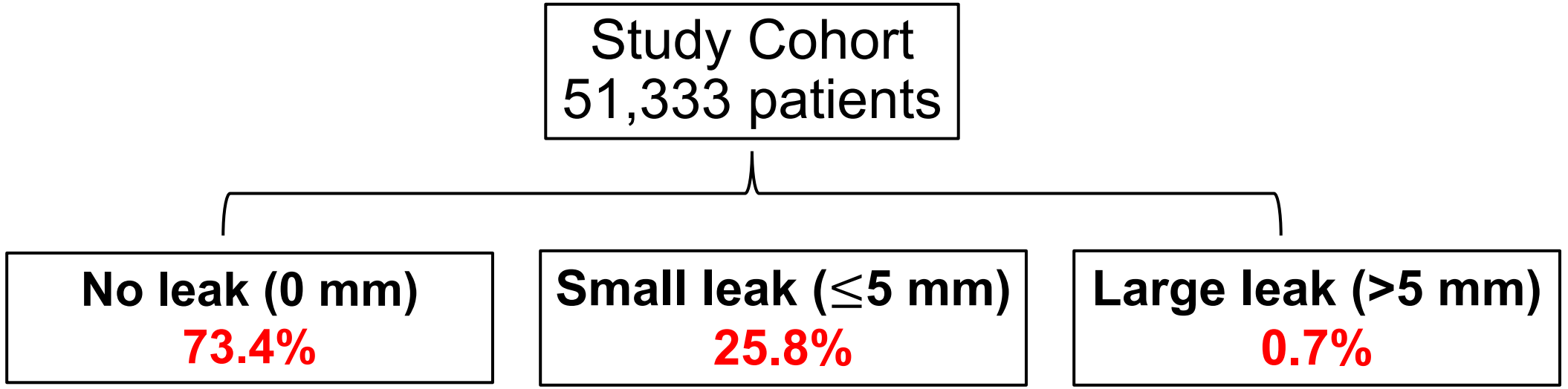
- ❑ Data collected at 45-day, 6-month, 1 & 2 years
- ❑ Automated ± manual adjudication
- ❑ Audits 5% of the sites annually*
  - 93.3% agreement with source documentation
  - 100% agreement with billing information
- ❑ Utilized for research via NCDR R&P process [1,2]
- ❑ Currently >120,000 LAAO cases recorded



[1] Freeman et al. JACC. 2020:7;75(13):1503-1518
[2] Darden et al. JAMA Cardiol. 2021:1;6(11):1275-1284
* Prior NCDR data audits

Residual leaks after LAAO: Insights from NCDR

Study Population & Endpoints



1º Endpoint: a composite of stroke, TIA, or systemic embolization

2º Endpoint: major bleeding, death, major adverse events

Residual leaks after LAAO: Insights from NCDR

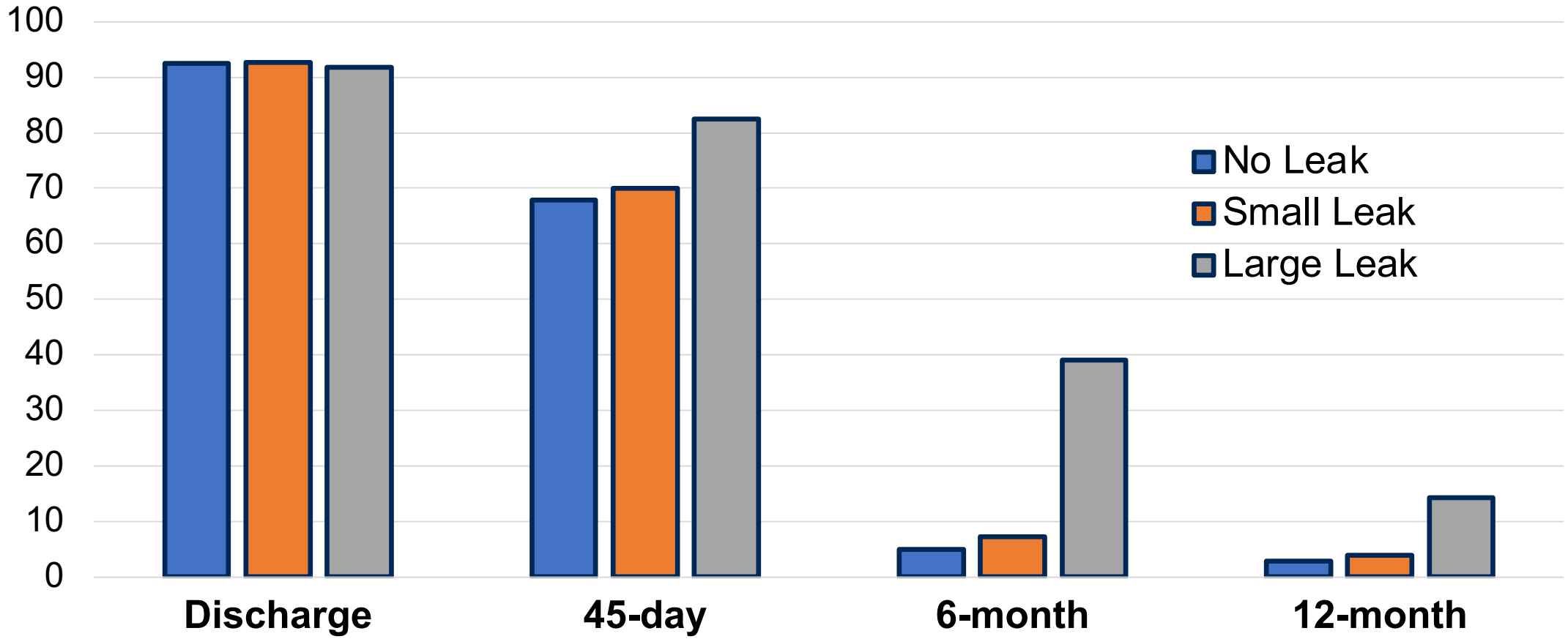
Baseline Characteristics

- Modest but statistically significant differences in baseline profile
- No difference in moderate sedation or ICE usage, case duration, contrast volume, or in-hospital complications

Patient Characteristics	No Leak	Small Leak	Large Leak	P value
Non-Paroxysmal AF	43.3%	48.2%	53.8%	<.001
Cardiomyopathy	19.8%	22.1%	24.0%	<.001
LAA orifice diameter	21.1±4.2	22.3±4.3	23.7±4.4	<.001

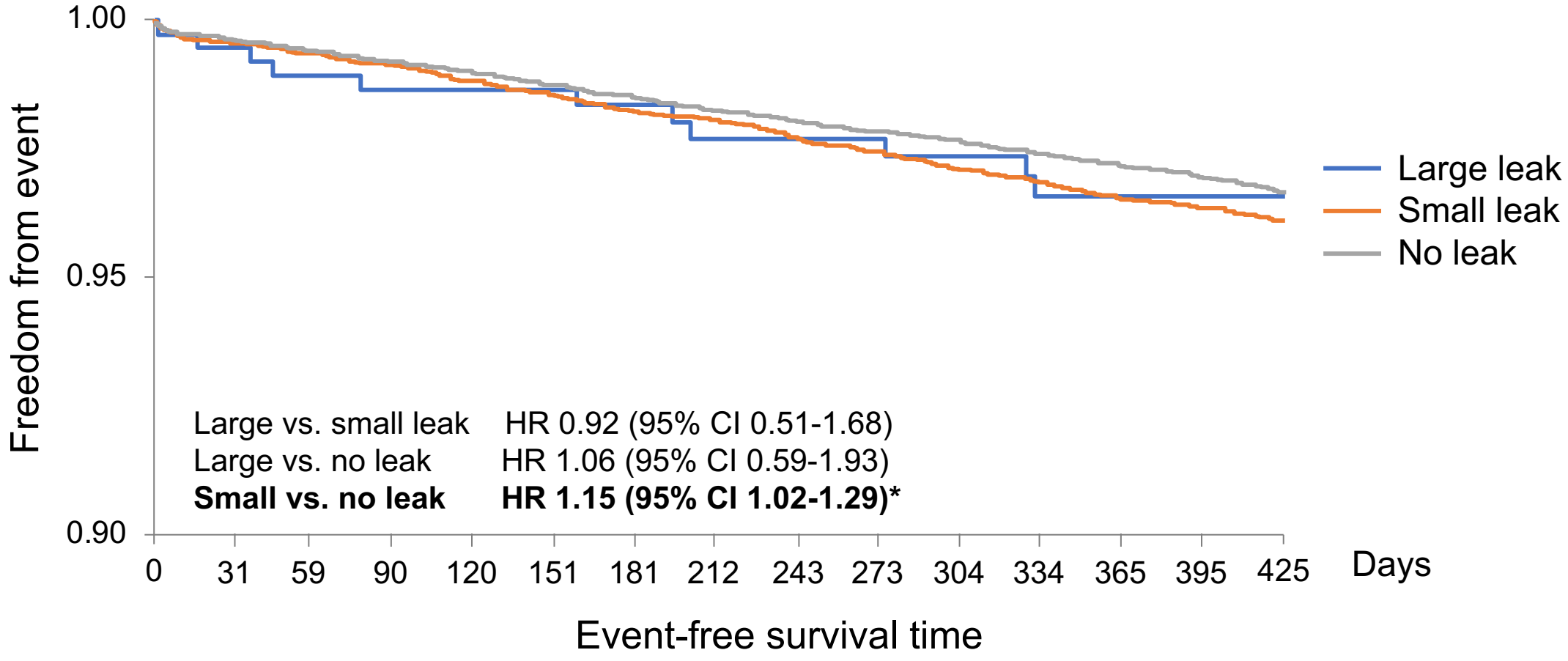
Residual leaks after LAAO: Insights from NCDR

Post-LAAO Anticoagulation



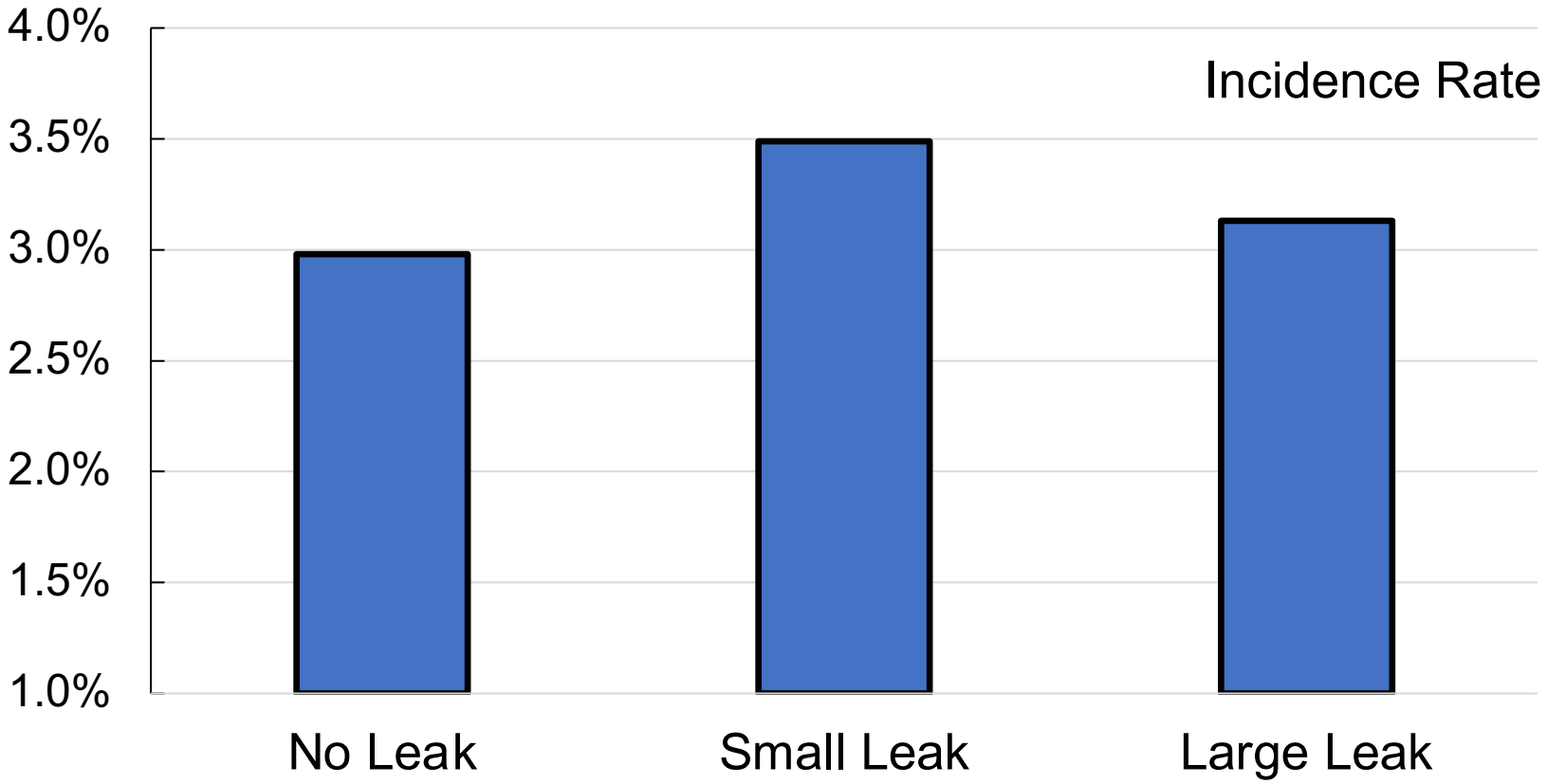
Residual leaks after LAAO: Insights from NCDR

1º Endpoint: Stroke, TIA, or SE



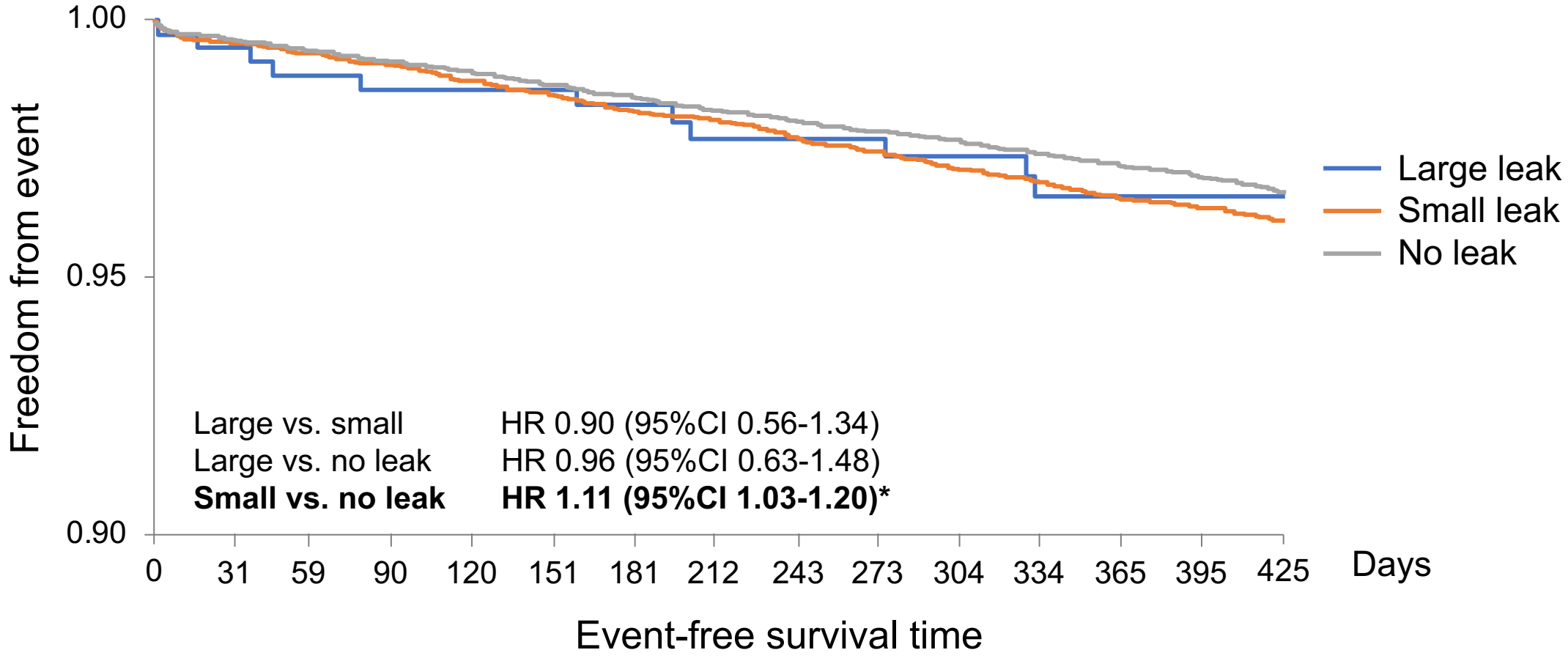
Residual leaks after LAAO: Insights from NCDR

1º Endpoint: Stroke, TIA, or SE



Residual leaks after LAAO: Insights from NCDR

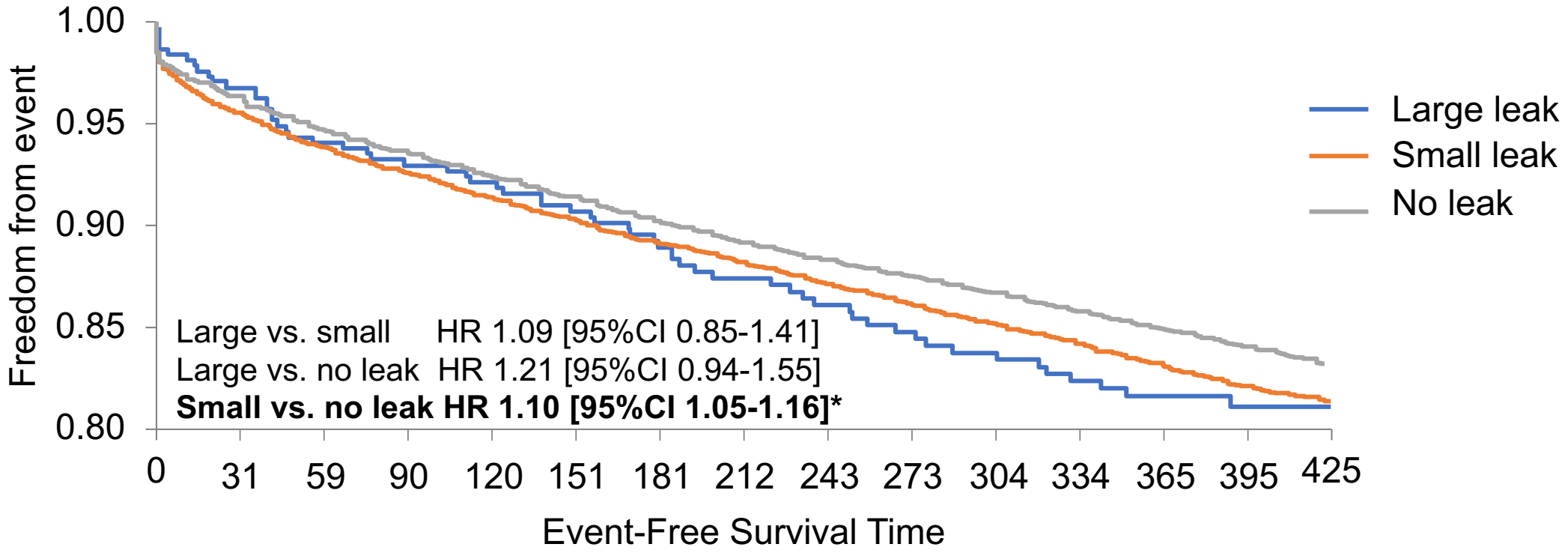
2º Endpoint: Major Bleeding*



* Major bleeding was defined as: access bleeding or hematoma, GI bleeding, retroperitoneal bleeding, other non-intracranial bleeding or hemothorax requiring hospitalization and/or causing >2 gram/deciliter decrease in hemoglobin and/or requiring transfusion

Residual leaks after LAAO: Insights from NCDR

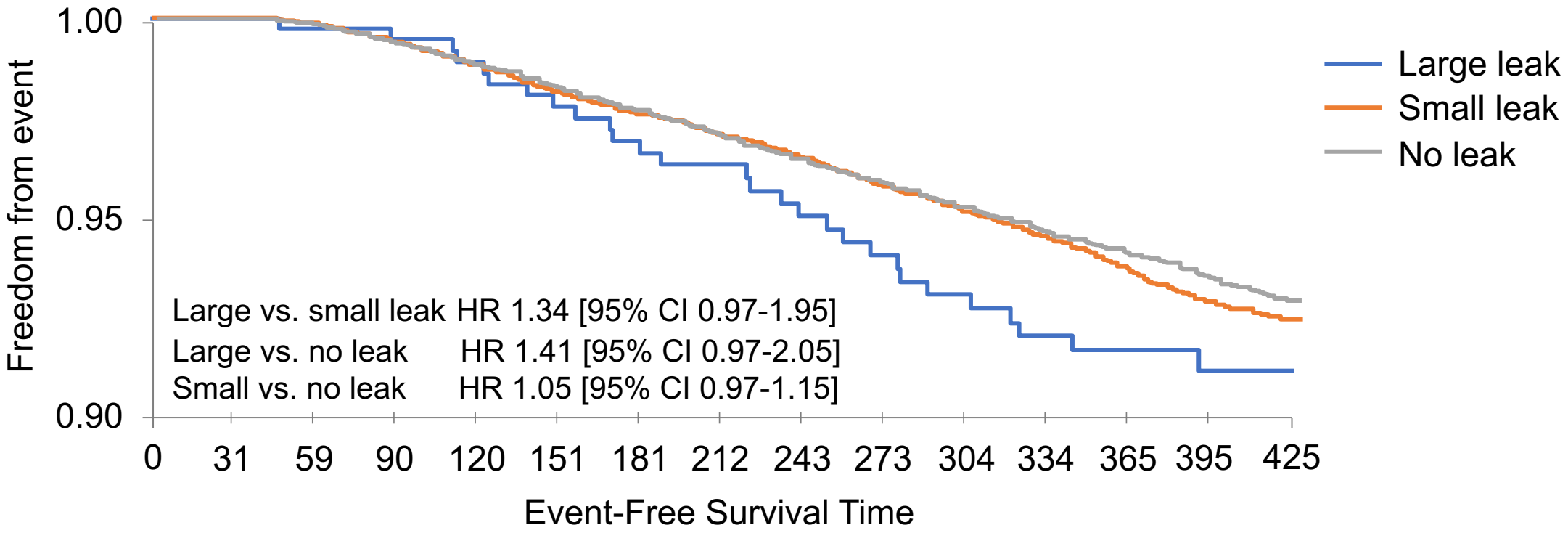
2º Endpoint: Major Adverse Events*



* Major adverse events included death; cardiac arrest; stroke; TIA; SE; major bleeding; major vascular complication, MI, pericardial effusion requiring intervention, or device embolization

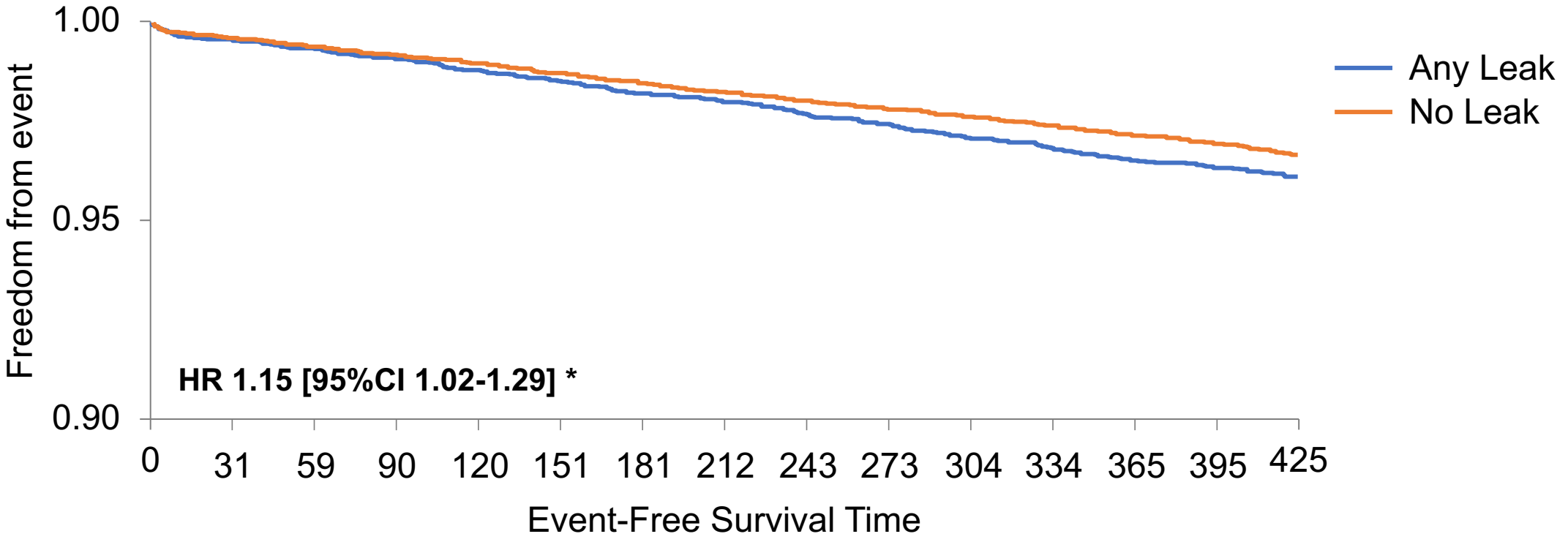
Residual leaks after LAAO: Insights from NCDR

2º Endpoint: All-cause death



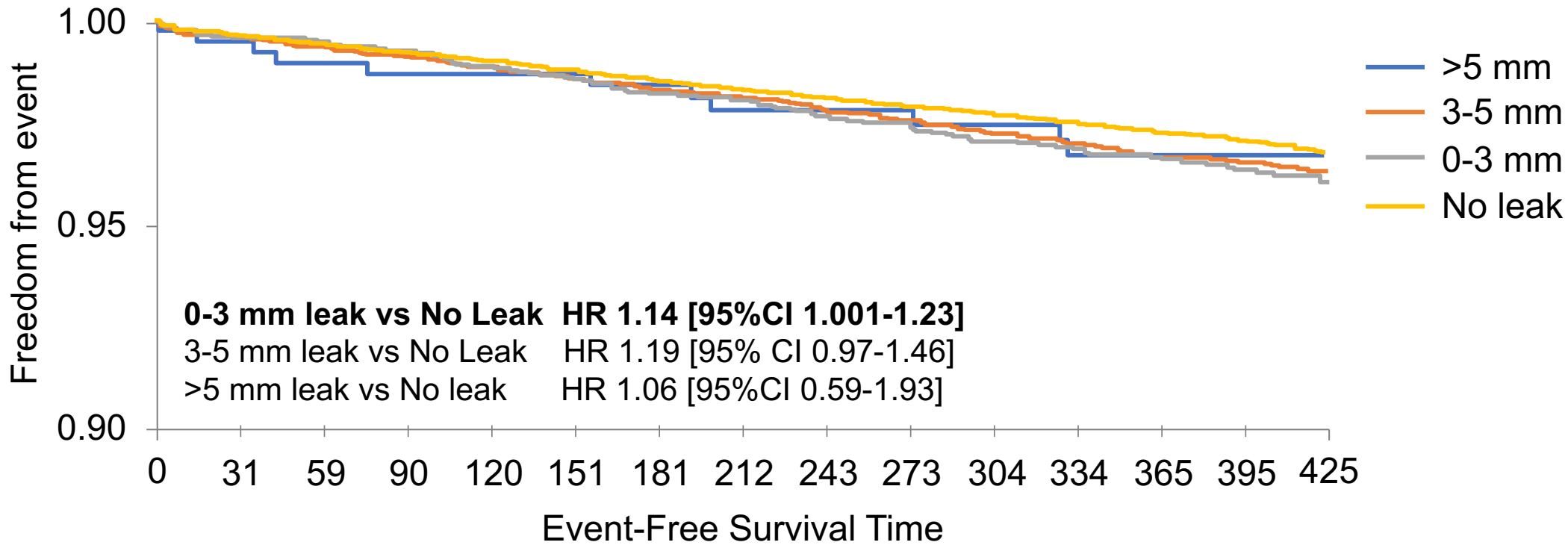
Residual leaks after LAAO: Insights from NCDR

Secondary Analysis: Stroke, TIA, SE



Residual leaks after LAAO: Insights from NCDR

Secondary Analysis: Stroke, TIA, SE



Limitations

- Observational registry
- Imaging for leak >45 day uncommon in practice
- Variation in peri-device leak size measurement
- Only the first-generation Watchman device included
- Data on interventional leak management not available
- Follow up limited to 1 year

Conclusions

- Peri-device leak at follow up is observed in ~25% of patients undergoing LAAO with the Watchman 2.5 device
- The leak was small ≤ 5mm in >99% of patients
- Small leaks were associated with a modest (~10-15%) increase in 1-year risk-adjusted rates of thromboembolic and bleeding complications

Clinical Impact of Residual Leaks Following Left Atrial Appendage Occlusion: Insights from the NCDR LAAO Registry

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Effects of empagliflozin on symptoms, physical limitations and quality of life in acute heart failure – results from the EMPULSE trial

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Disclosures

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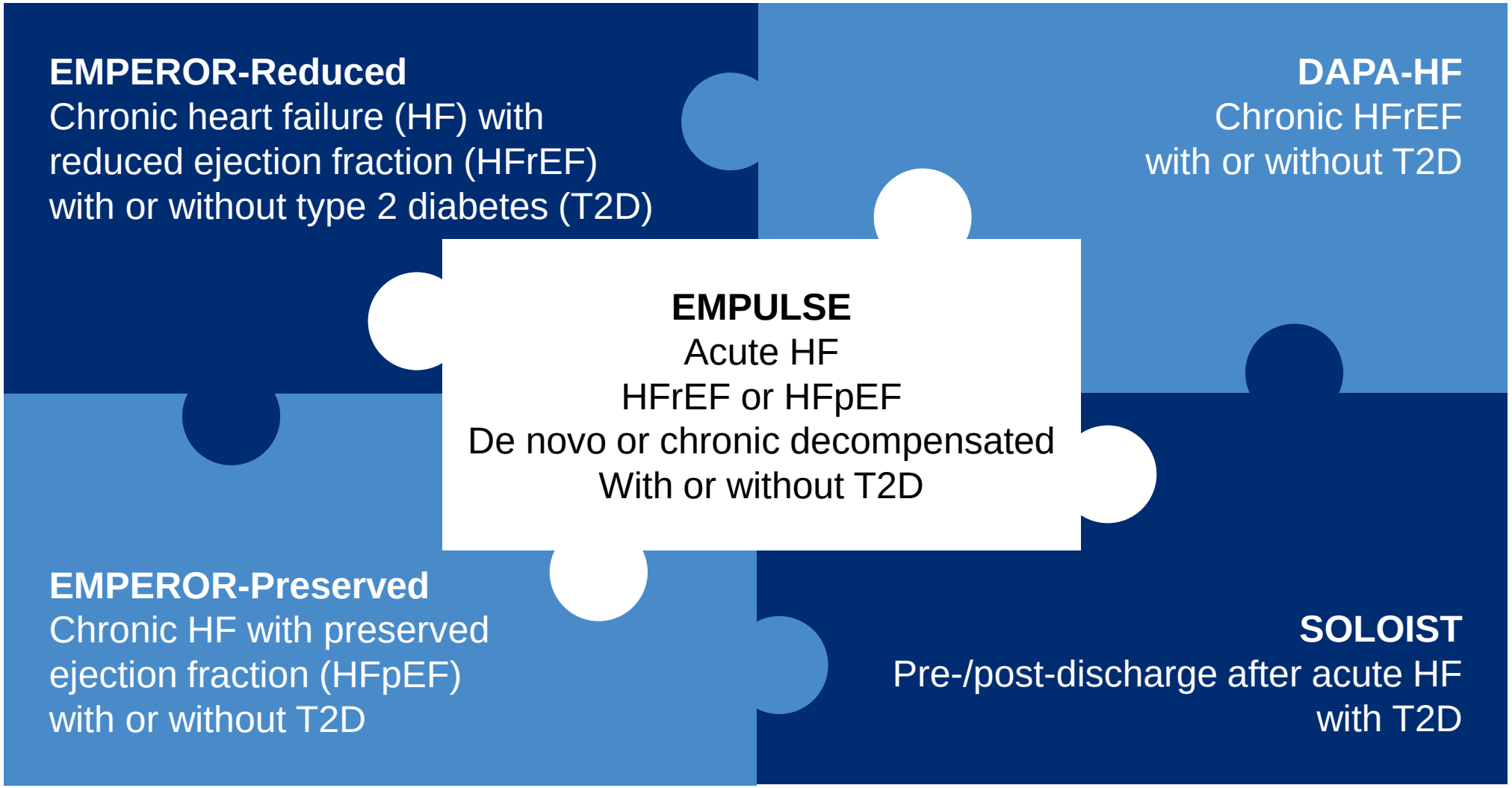
Background

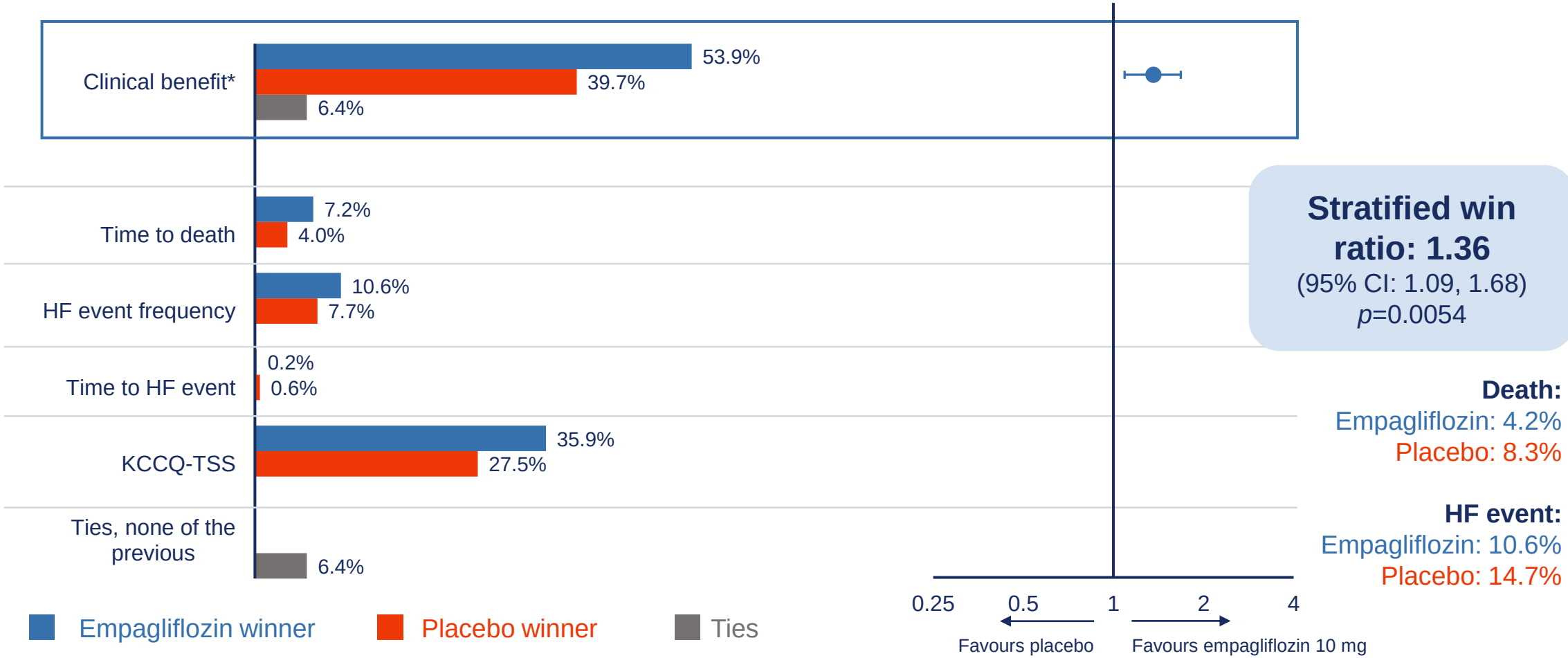
- Patients hospitalized for acute heart failure (AHF) experience poor health status, including high burden of symptoms and physical limitations, and poor quality of life
- Improving health status is a key goal of management
- To date, there has been a lack of therapies with compelling benefit on these outcomes in AHF, highlighting a critical unmet need
- Sodium-glucose-cotransporter-2 (SGLT2) inhibitors improve health status in chronic heart failure, but their effects in AHF have not been well characterized

EMPULSE: the missing link



HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes.

EMPULSE main results



Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Death:
Empagliflozin: 4.2%
Placebo: 8.3%

HF event:
Empagliflozin: 10.6%
Placebo: 14.7%

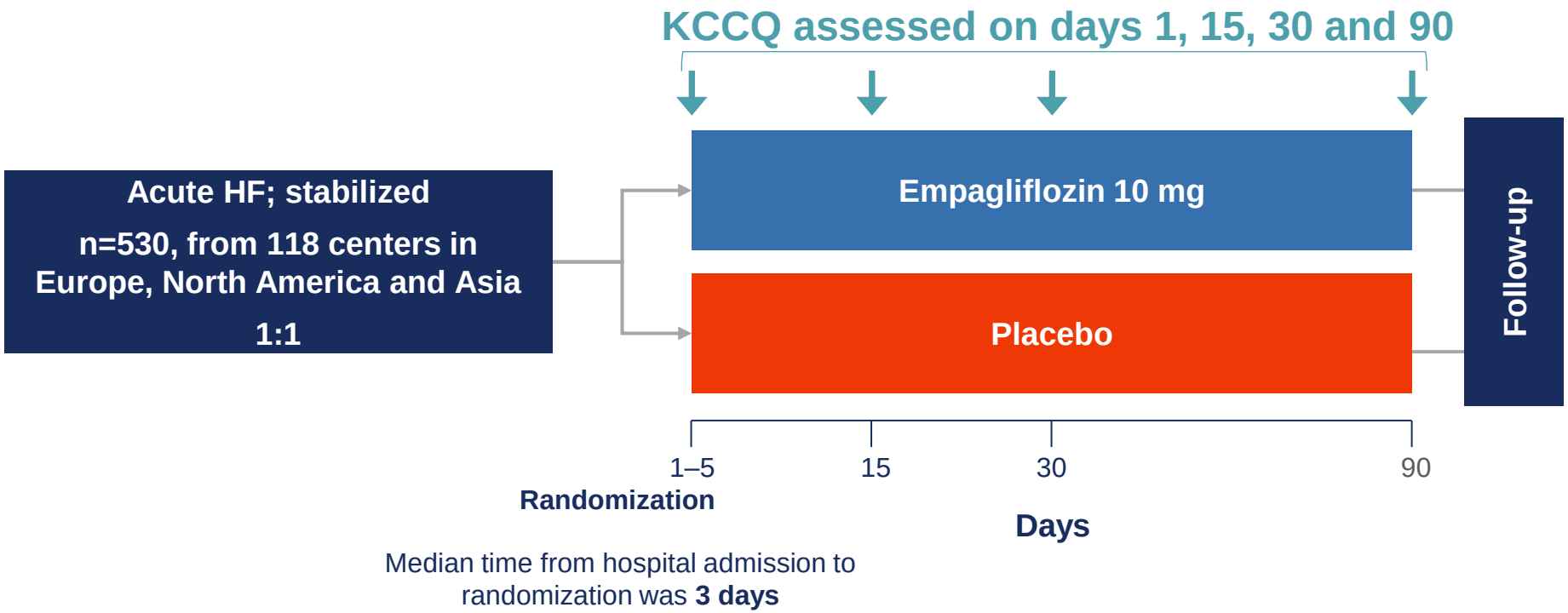
Numbers reflect percentage of comparisons. For the components of the win ratio these numbers do not reflect randomized comparisons. *Composite of death, number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits), time to first HFE and ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment. CI, confidence interval; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Voors AA *et al. Nat Med.* 2022;doi:10.1038/s41591-021-01659-1.

Objectives of this EMPULSE analysis

- Evaluate the effects of empagliflozin on the primary endpoint of total clinical benefit in the EMPULSE trial according to the degree of symptomatic impairment at baseline

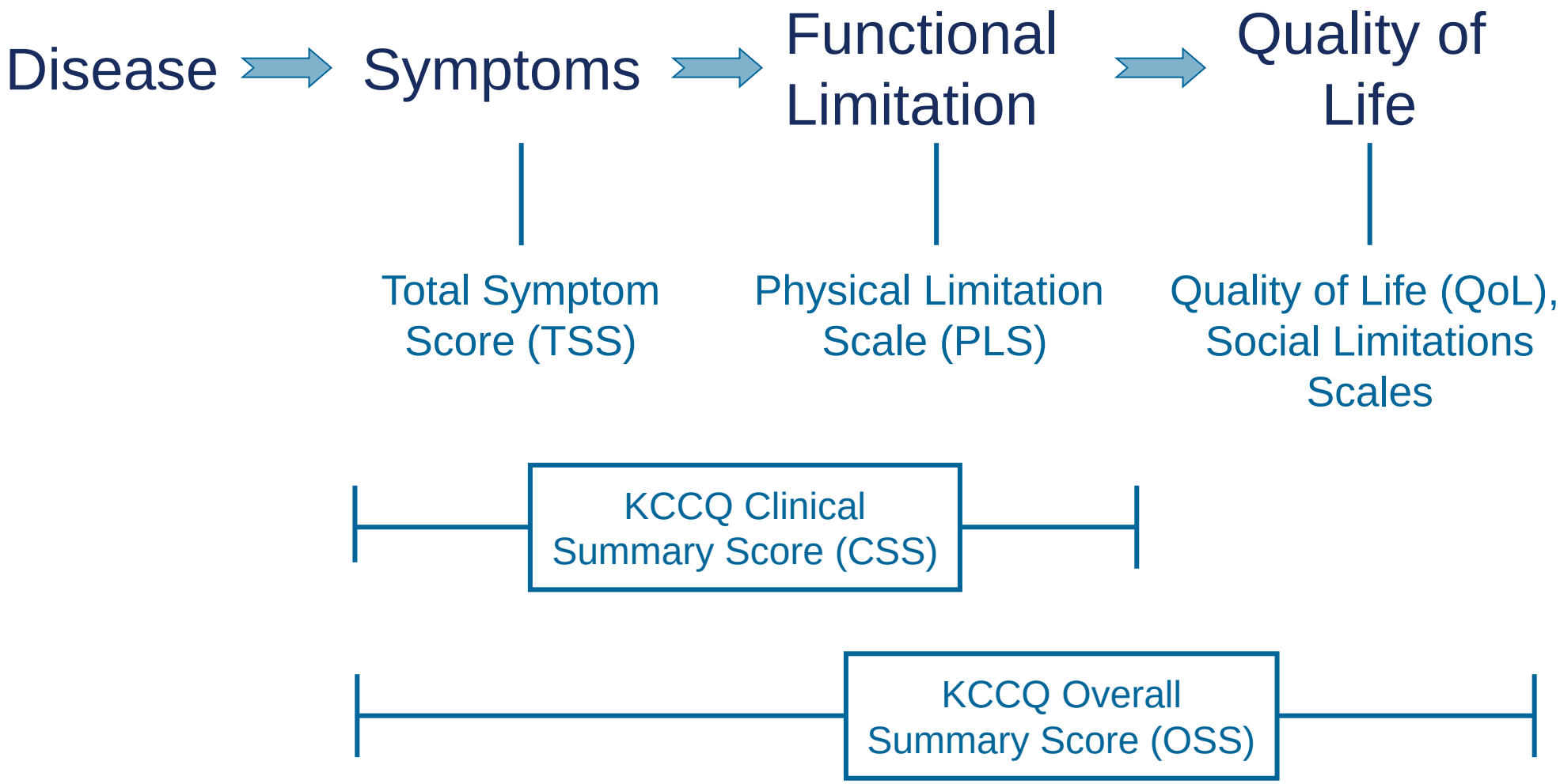
- Examine the impact of empagliflozin on the broad range of health status outcomes, as measured by various domains of the Kansas City Cardiomyopathy Questionnaire (KCCQ), and time course of these effects

EMPULSE study design[1,2]



1. Tromp J *et al. Eur J Heart Fail.* 2021;23:826; 2. Voors AA *et al. Nat Med.* 2022;doi:10.1038/s41591-021-01659-1.

Mapping the KCCQ scales



Statistical analysis

- Patients stratified based on baseline KCCQ-TSS tertiles
- Effects of empagliflozin on the primary endpoint across the KCCQ tertiles evaluated using win ratio with Cochran's Q statistic (*post hoc*)
- Between-group differences in KCCQ domains at 15, 30 and 90 days assessed using mixed models for repeated measures, adjusted for heart failure status and baseline KCCQ (pre-specified)
- Responder analyses compared proportions of patients with a deterioration, and clinically meaningful improvements in KCCQ-TSS at 90 days using logistic regression models (pre-specified and *post hoc*)

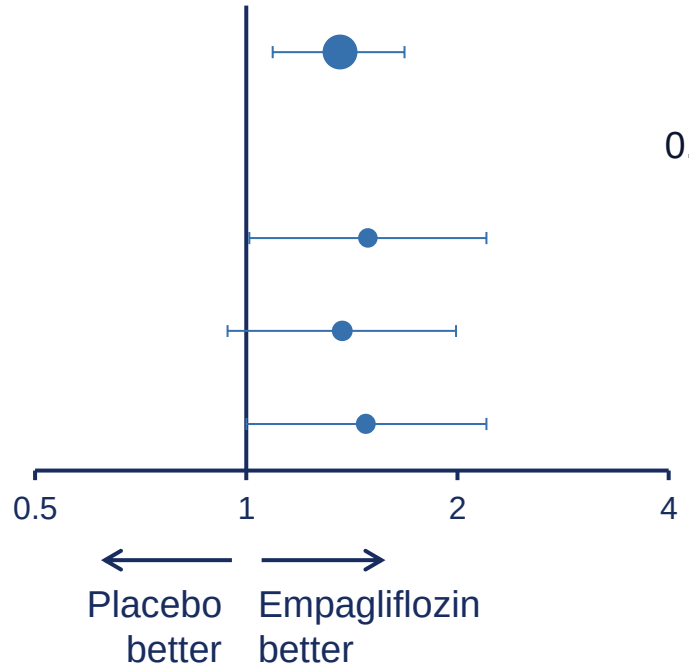
Baseline characteristics of the EMPULSE study population by tertiles of KCCQ

			KCCQ-TSS at baseline				*p*-value for trend
			Tertile 1 (n=166)	Tertile 2 (n=184)	Tertile 3 (n=176)	Total (n=526)	
Demographic characteristics	Age, years, mean (SD)		66.5 (13.4)	69.5 (12.9)	69.4 (13.3)	68.5 (13.3)	0.04
	Sex, female n (%)		68 (41)	59 (32)	50 (28)	177 (34)	0.01
	Race, n (%)	White	130 (78)	150 (82)	129 (73)	409 (78)	<0.001
		Black/African-American	22 (13)	19 (10)	13 (7)	54 (10)	
		Asian	11 (7)	12 (7)	34 (19)	57 (11)	
		Other	2 (1)	3 (2)	0	5 (1)	
Medical history	T2D, n (%)		93 (56)	78 (42)	66 (38)	237 (45)	<0.001
	Atrial fibrillation, n (%)		84 (51)	92 (50)	84 (48)	260 (49)	0.59
HF characteristics	HF status, n (%)	De novo	43 (26)	65 (35)	66 (38)	174 (33)	0.02
		Decompensated chronic	123 (74)	119 (65)	110 (62)	352 (67)	
	LVEF, n (%)	≤40%	108 (65)	119 (65)	125 (71)	352 (67)	0.30
		>40%	55 (33)	62 (34)	50 (28)	167 (32)	
	NYHA class, n (%)	II	26 (16)	76 (41)	84 (48)	186 (35)	<0.001
		III–IV	138 (83)	106 (58)	82 (47)	326 (62)	
	KCCQ-TSS (points), mean (SD)		14.4 (7.8)	37.9 (7.3)	68.8 (12.6)	40.8 (24.0)	<0.001
Laboratory values	eGFR, mL/min per 1.73 m^2, mean (SD)		52.8 (20.9)	55.1 (20.6)	54.2 (19.5)	54.1 (20.3)	0.57
	NT-proBNP, pg/mL, median (IQR)		3687.3 (2143.9–6446.8)	3188.7 (1725.2–5936.8)	2520.2 (1463.1–6012.9)	3245.8 (1735.4–6104.3)	<0.01
Heart failure treatments	ACEi/ARB/ARNI, n (%)		107 (64)	136 (74)	125 (71)	368 (70)	0.19
	Beta-blocker, n (%)		136 (82)	137 (74)	145 (82)	418 (79)	0.88
	MRA, n (%)		83 (50)	89 (48)	102 (58)	274 (52)	0.13
	Diuretics other than MRA, n (%)		144 (87)	154 (84)	143 (81)	441 (84)	0.17

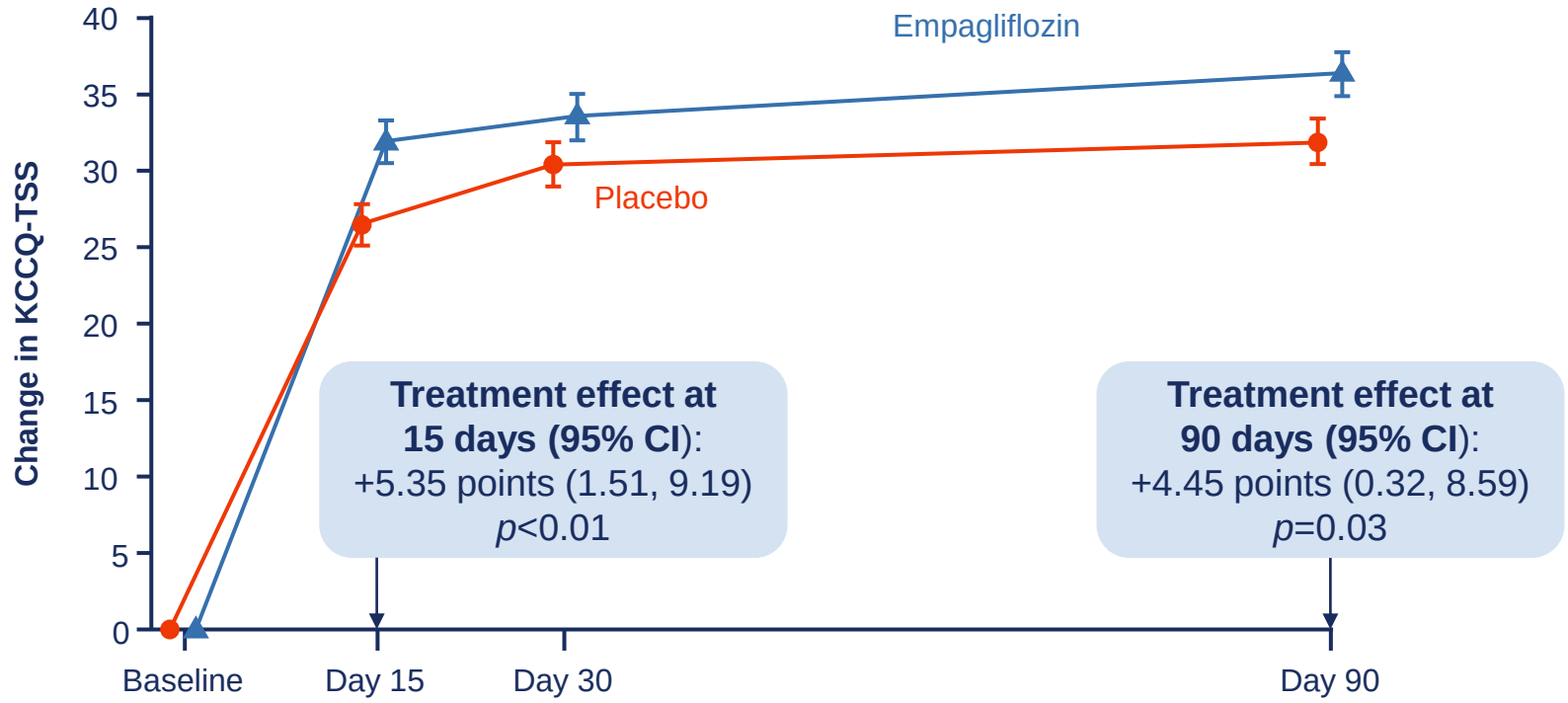
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NHYA, New York Heart Association.

Effects of empagliflozin versus placebo on the primary hierarchical composite endpoint of clinical benefit across tertiles of KCCQ-TSS

Subgroup	N analysed		Win ratio (95% CI)	Interaction *p*-value
Category	Empagliflozin 10 mg	Placebo		
All patients	265	265	1.36 (1.09,1.68)	
Baseline KCCQ-TSS				0.94
<27.1	84	82	1.49 (1.01, 2.20)	
≥27.1 and <52.1	93	91	1.37 (0.94, 1.99)	
≥52.1	85	91	1.48 (1.00, 2.20)	

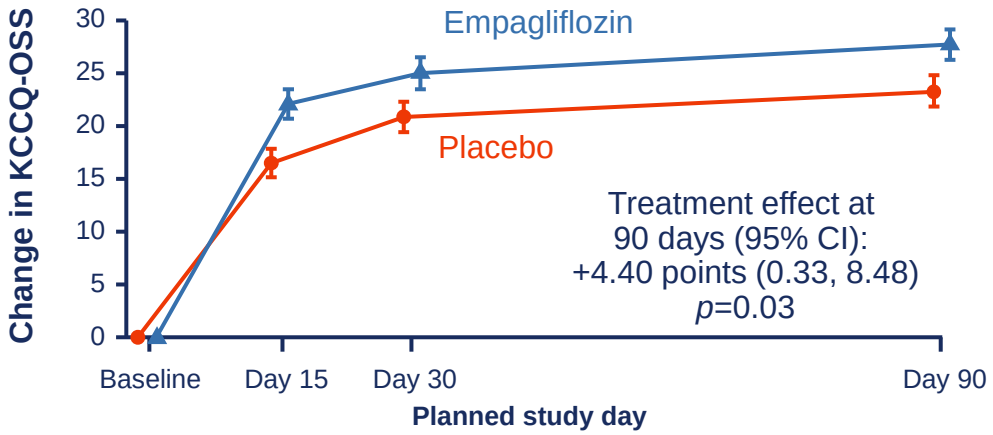


Effects of empagliflozin versus placebo on change in KCCQ-TSS

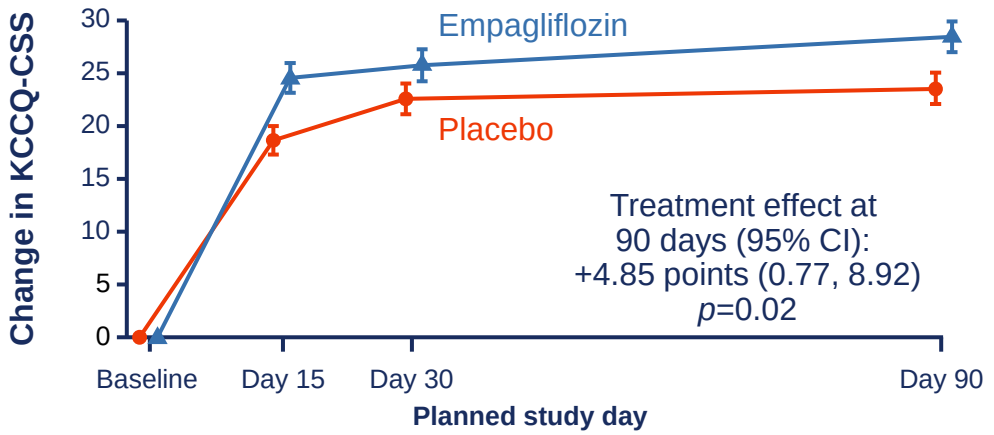


N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

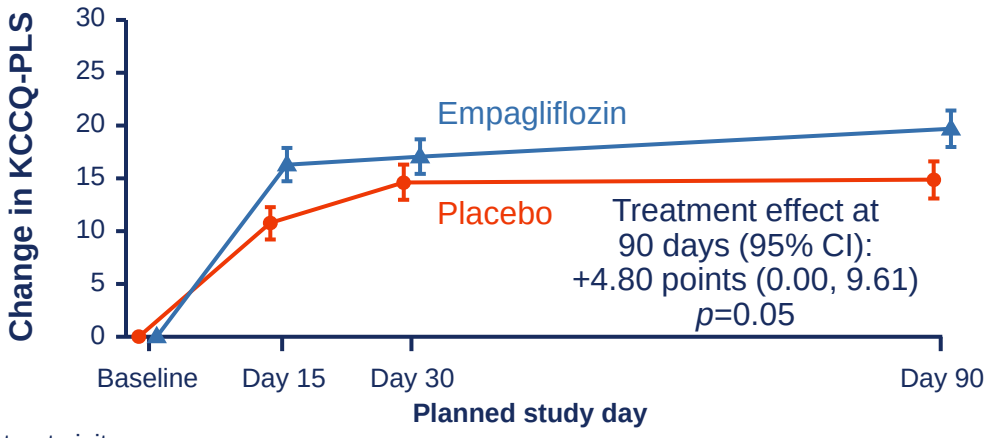
Effects of empagliflozin versus placebo on change in KCCQ-OSS, -CSS, -PLS and -QoL



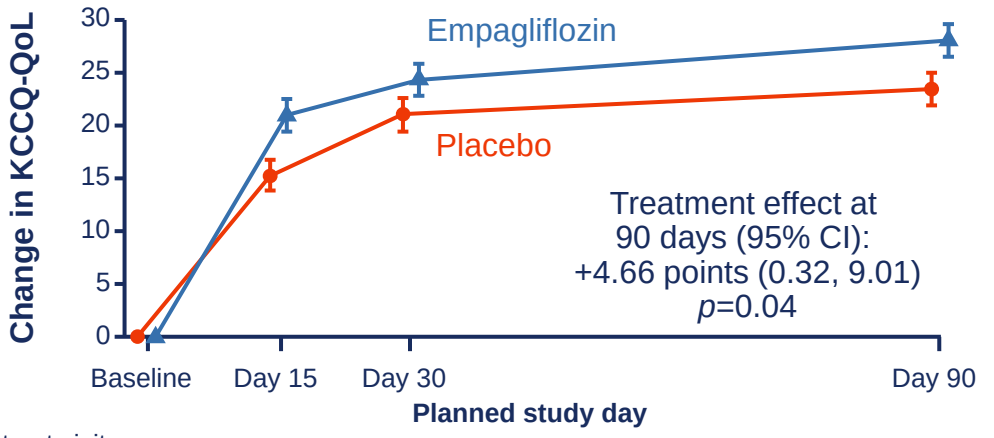
N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230



N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

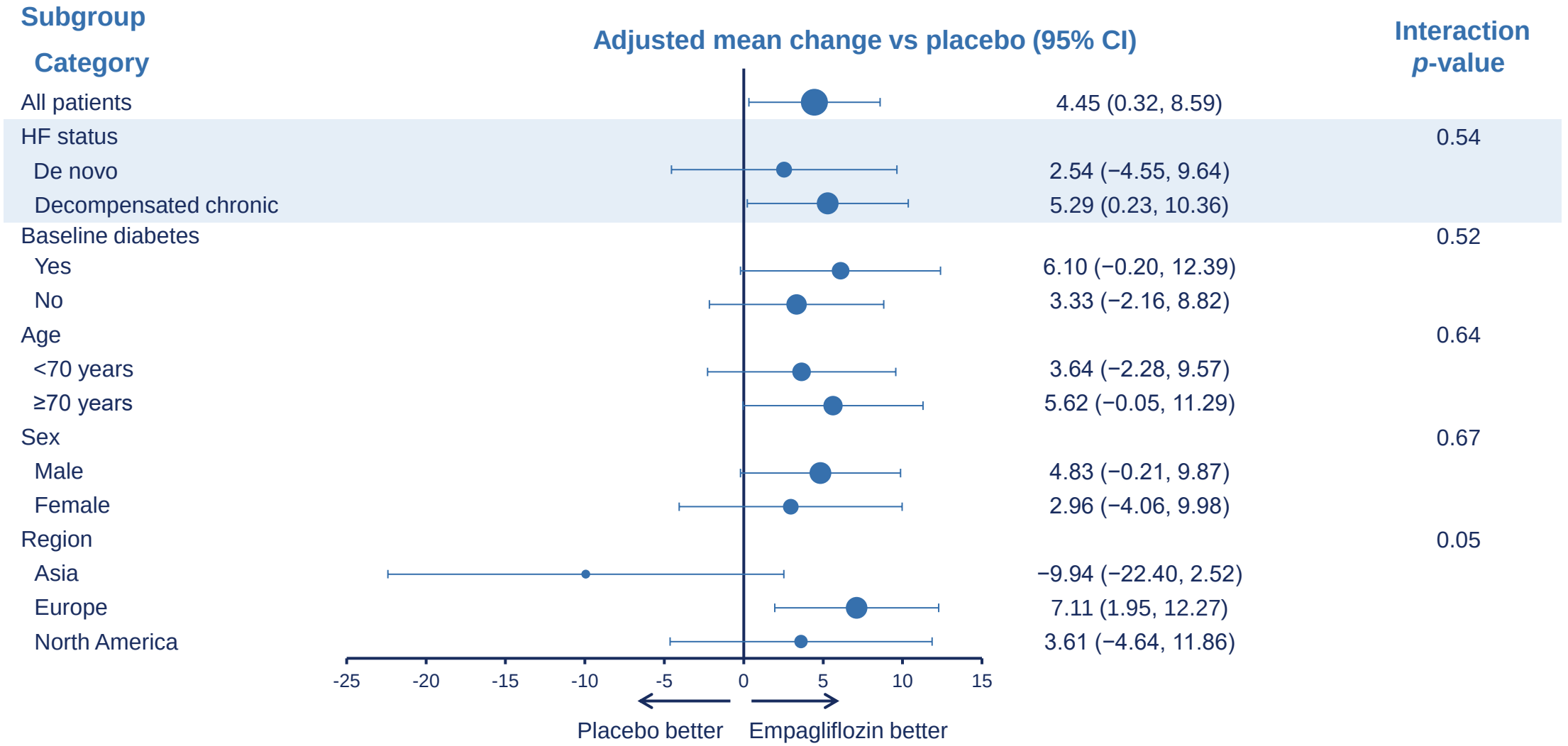


N with data at visit				
Placebo	245	232	225	217
Empagliflozin	240	225	228	225

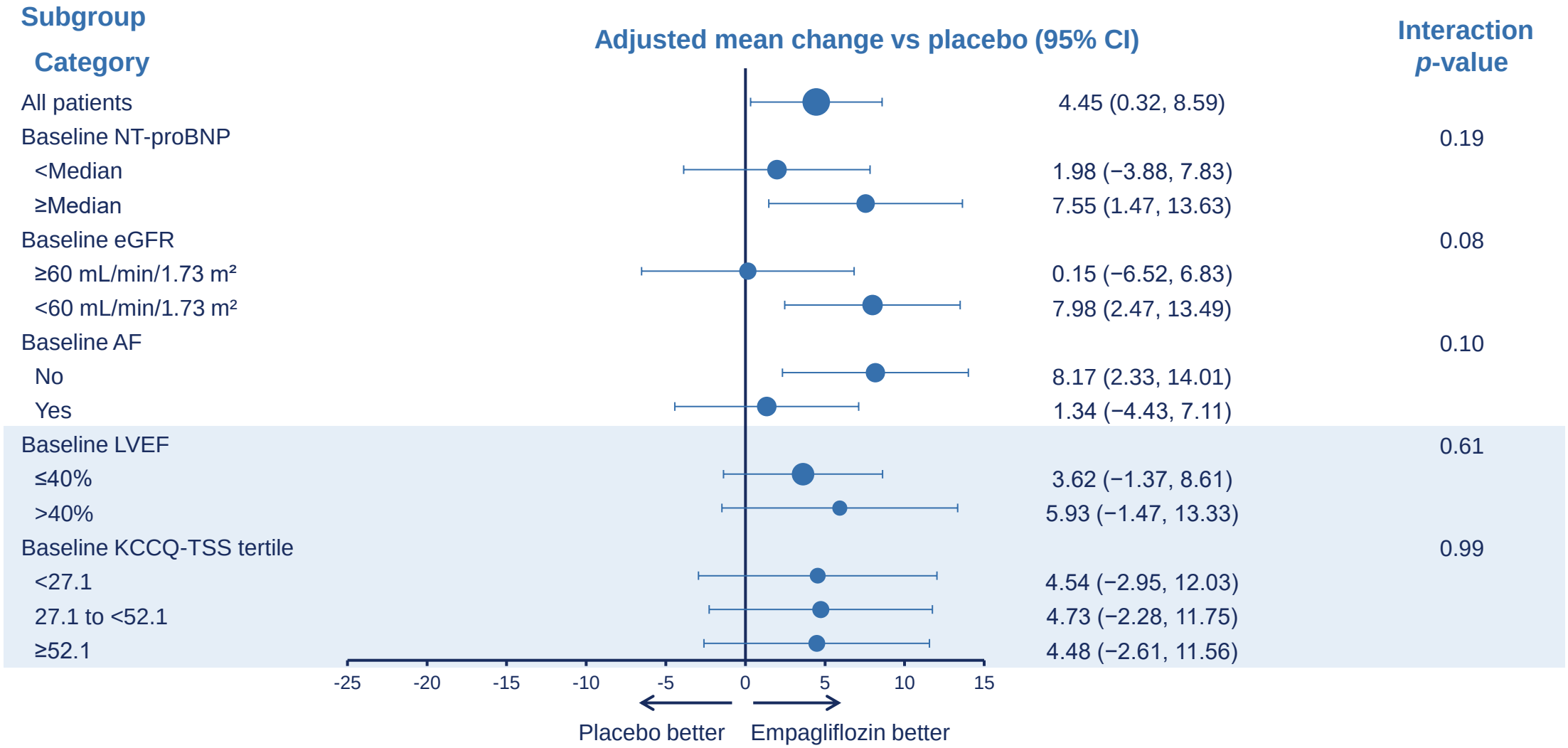


N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

Effects of empagliflozin versus placebo on KCCQ-TSS at Day 90 across pre-specified subgroups (1/2)

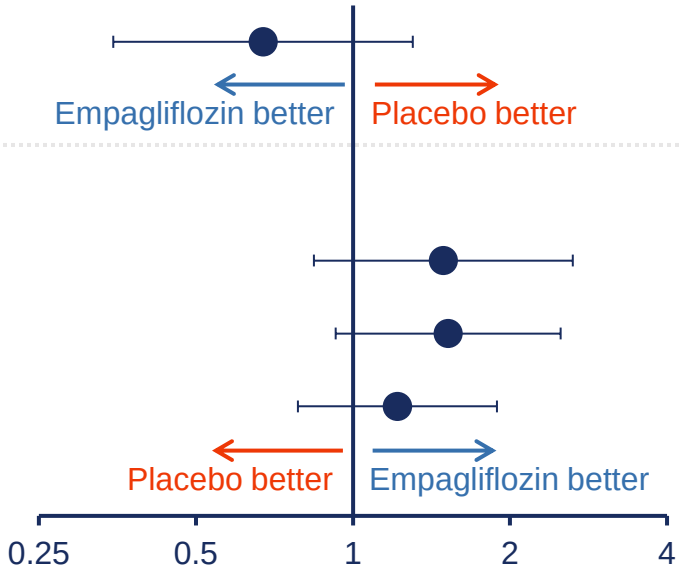


Effects of empagliflozin versus placebo on KCCQ-TSS at Day 90 across pre-specified subgroups (2/2)



Responder analysis for KCCQ-TSS deterioration and improvements at Day 90

	Odds ratio (95% CI)	Odds ratio (95% CI)	*p*-value
Deterioration at 90 days			
≥5 points		0.67 (0.35, 1.30)	0.24
Improvement at 90 days			
≥5 points		1.49 (0.84, 2.64)	0.17
≥10 points		1.52 (0.93, 2.50)	0.10
≥20 points		1.22 (0.78, 1.89)	0.38



Limitations

- Although KCCQ-TSS was a pre-defined secondary endpoint, and prospective assessments of KCCQ domains were pre-specified, several of the analyses were done *post hoc*

- The relatively modest sample size of this study did not provide sufficient power for the responder analyses

Conclusions

- Treatment with empagliflozin produced total clinical benefit among patients hospitalized with AHF across the entire range of KCCQ
  - Indicates that the benefits of empagliflozin in this patient group are independent of symptomatic impairment at baseline
- Empagliflozin significantly improved all key KCCQ domains (which collectively encompass symptoms, physical function, quality of life, and social function)
- Benefits generally consistent across demographic and clinical characteristics, seen as early as 15 days, and maintained through 90 days

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EFFECTS OF EMPAGLIFLOZIN ON SYMPTOMS, PHYSICAL LIMITATIONS AND QUALITY OF LIFE IN PATIENTS HOSPITALIZED FOR ACUTE HEART FAILURE – RESULTS FROM THE EMPULSE TRIAL

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Study Team: Claudia Grauer, Rosa-Maria Espadero, Jon P Blatchford, Rafael Sani-Simoes MD.

AMERICAN COLLEGE of CARDIOLOGY®

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EMPULSE

Effects of Empagliflozin on Symptoms, Physical Limitations and Quality of Life in Patients Hospitalized for Acute Heart Failure

Prospective, Multicenter Trial

OBJECTIVE: To investigate the effects of empagliflozin, an SGLT2 inhibitor, on symptoms, physical limitations, and quality of life in the EMPULSE trial, which investigated empagliflozin among individuals hospitalized with acute heart failure (HF).

530 PATIENTS

INCLUSION CRITERIA: Hospitalization with acute HF with randomization between 24 hours and 5 days after admission without hypotension or inotropic support and with elevated natriuretic peptide levels.

EMPAGLIFLOZIN (N=265)

VS.

PLACEBO (N=265)

PRIMARY ENDPOINT

Clinical benefit at 90 days, defined as a composite endpoint of time to all-cause death, number of HF events, time to first HF event, and a 5-point or greater difference in change in KCCQ-TSS, was greater in patients treated with empagliflozin vs placebo; Win ratio 1.36 (1.09 – 1.68), $P_{interaction}$ by baseline KCCQ-TSS = 0.94.

CONCLUSION

A net clinical benefit was observed at 90 days in patients hospitalized for acute HF after initiation of empagliflozin independent of baseline health status.

Kosiborod M, Angermann CE, Collins S, et al. Effects of Empagliflozin on Symptoms, Physical Limitations and Quality of Life in Patients Hospitalized for Acute Heart Failure. *Circulation* 2022; Apr 4: [Epub ahead of print].

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